New Product Development Pipeline Management

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Overview of Module

- New Product Development Management 50 min
  - Pharmaceutical Product R&D Pipeline
  - Decision criteria
- Break (5 min)
- Mathematical Programming Approaches 50 min
- Break (10 min)
- Tutorial on Discrete Event Simulation 30 min
- Simulation-based Approaches 50 min
- Break (5 min)
- PPD demonstration problems & student exercises 30 min
- Summary & Future Directions 10 min

Outline

- New Product Development Pipeline
  - Issues & features
- Pharmaceutical Product Pipeline
  - Special characteristics
  - Strategic & tactical decisions
  - Types of Uncertainties
- Decision Criteria
  - Economic
  - Risk metrics
  - Real Options Valuation
- Summary

Product Development Pipeline

Supply Chain for realization of new products

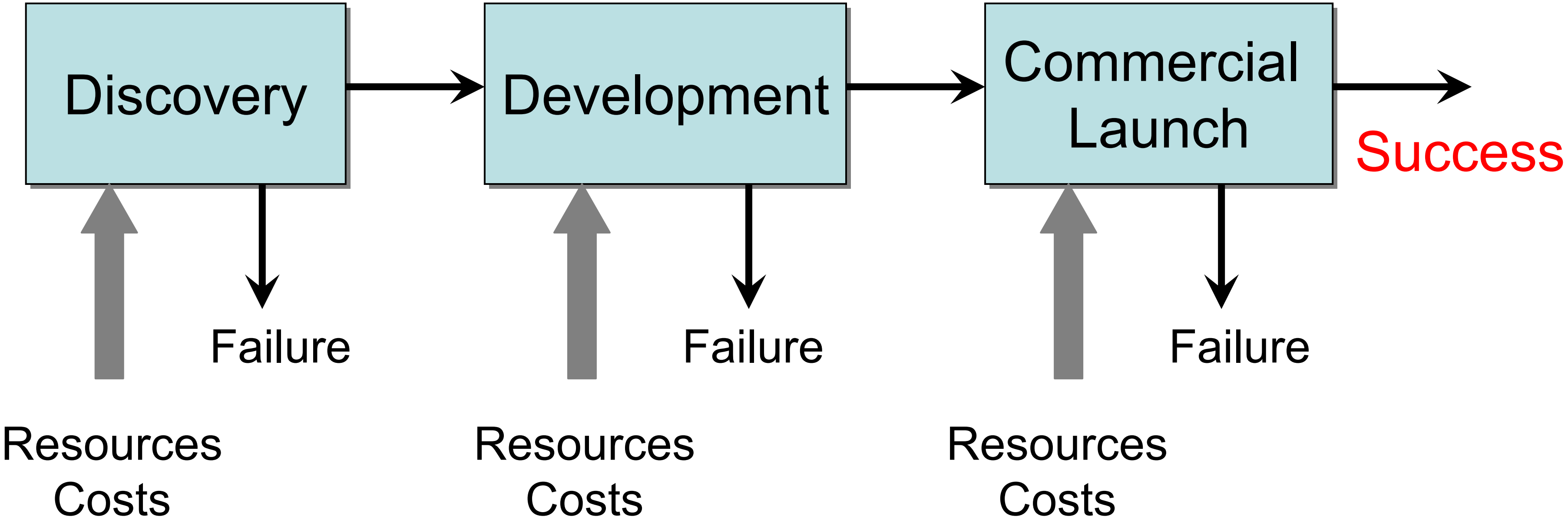
US Industry Average Performance

- 1 commercial success per 7 concepts in development
- 60% of new products launched are commercial success
- 50% of new product development resources spent on failed or cancelled products

Griffin (1997)

Product Development Pipeline

Multi-stage decision problem under uncertainty



Discovery

Development

Commercial Launch

Success

Failure

Failure

Failure

Resources
Costs

Resources
Costs

Resources
Costs

Key issues: Which projects to develop? In what order?
Level of resources to assign?
When to terminate development?

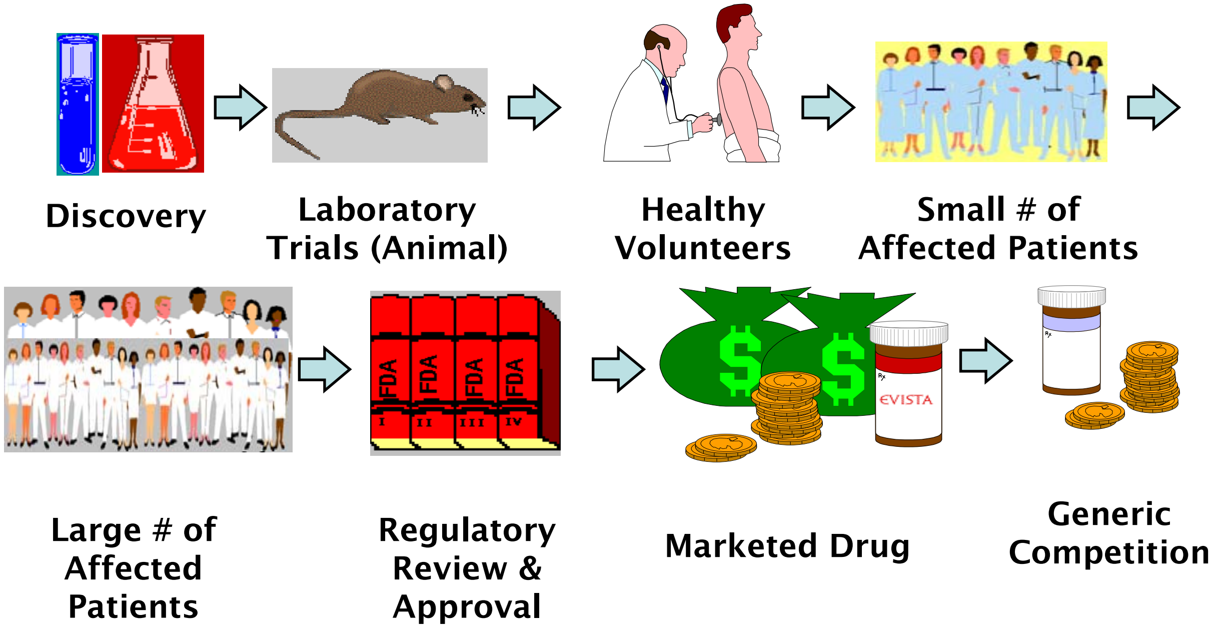
Related Problems & Literature

Financial Management & Operations Research

- Strategic components
  - Capital budgeting
  - Investment portfolio management
  - Capacity Planning
- Tactical components
  - Resource constrained project scheduling
  - Task sequencing, mode selection & scheduling

Life Cycle of New Drug Product

Highly Regulated - High Risk - High Payoff



Discovery

Laboratory Trials (Animal)

Healthy Volunteers

Small # of Affected Patients

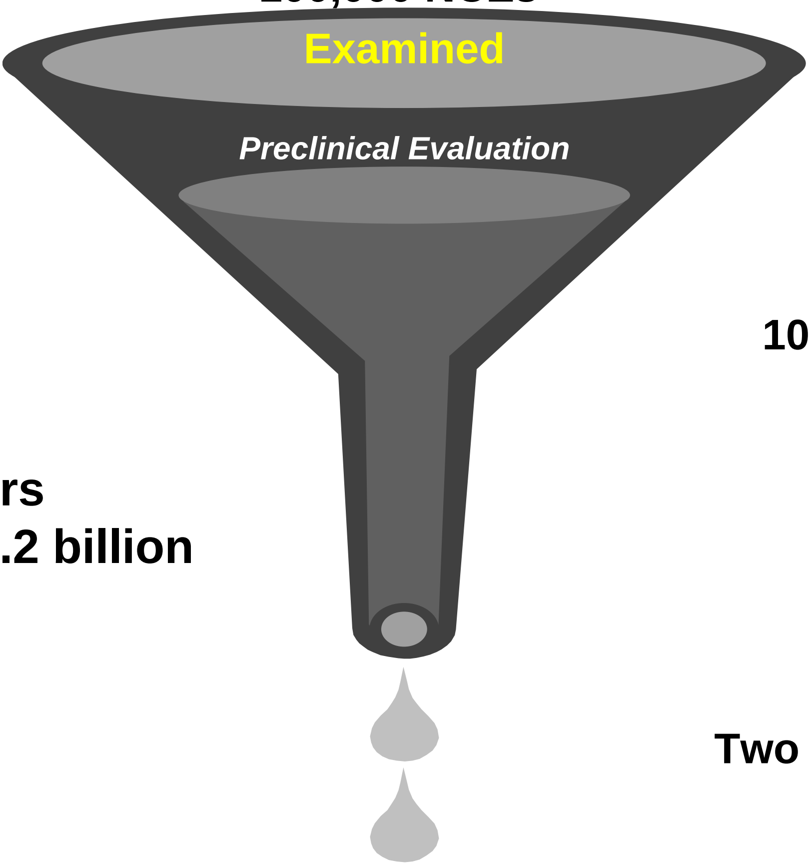
Large # of Affected Patients

Regulatory Review & Approval

Marketed Drug

Generic Competition

Attrition Rate of New Chemical Drug Entities



100,000 NCEs

Examined

Preclinical Evaluation

100 tested in humans

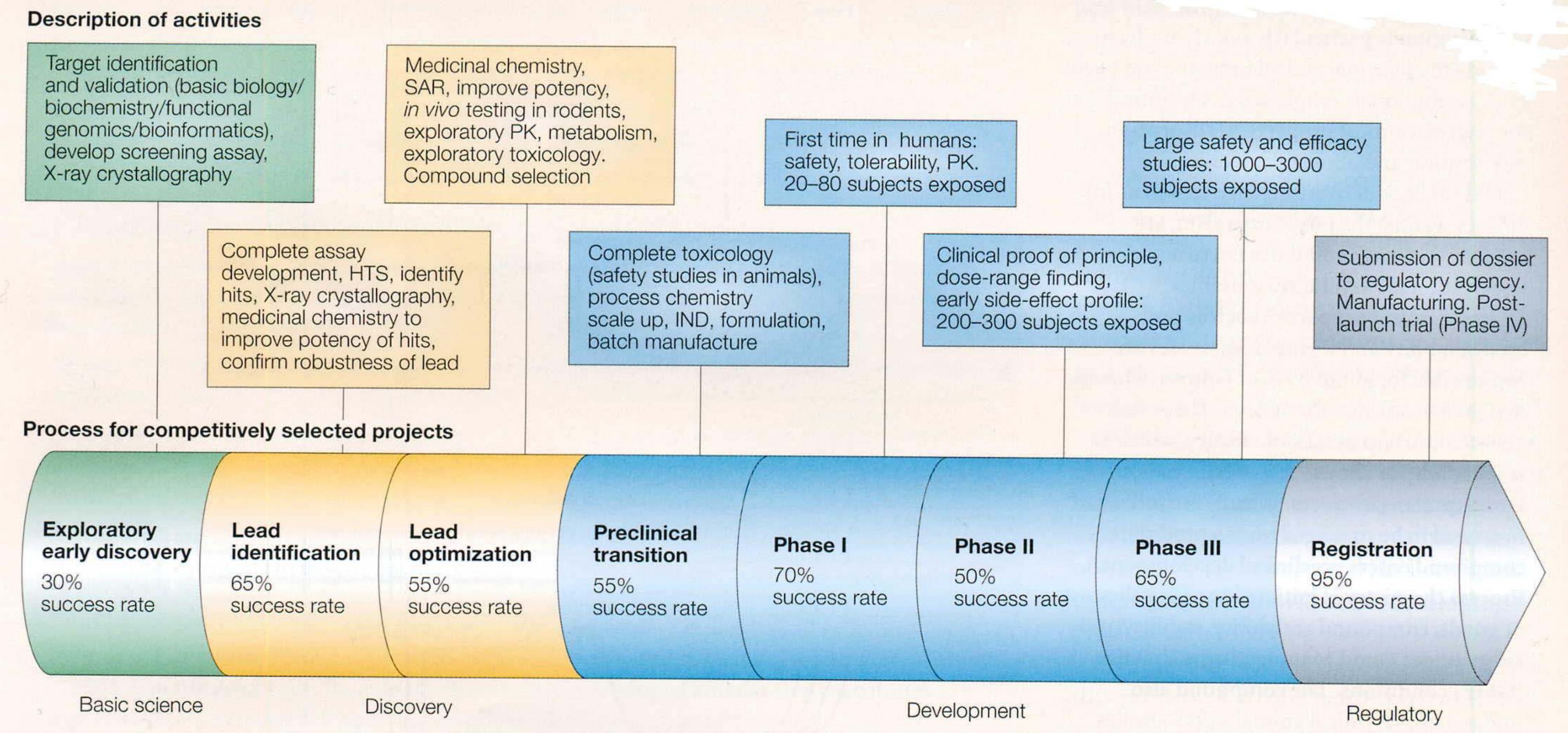
10 Marketed Drugs

6 to 12 Years
$600 million to $1.2 billion

Two Drugs Return a Profit

J. A. DiMasi, R. W. Hanson, H. G. Grabowski, L. Lasagna (1991). the Cost of Innovation in the Pharmaceutical Industry. J. Health Econom. 10:107-142.

Drug Discovery & Development Process



Description of activities

Target identification and validation (basic biology/ biochemistry/functional genomics/bioinformatics), develop screening assay, X-ray crystallography

Complete assay development, HTS, identify hits, X-ray crystallography, medicinal chemistry to improve potency of hits, confirm robustness of lead

Medicinal chemistry, SAR, improve potency, *in vivo* testing in rodents, exploratory PK, metabolism, exploratory toxicology. Compound selection

Complete toxicology (safety studies in animals), process chemistry scale up, IND, formulation, batch manufacture

First time in humans: safety, tolerability, PK. 20–80 subjects exposed

Clinical proof of principle, dose-range finding, early side-effect profile: 200–300 subjects exposed

Large safety and efficacy studies: 1000–3000 subjects exposed

Submission of dossier to regulatory agency. Manufacturing. Post-launch trial (Phase IV)

Process for competitively selected projects

Exploratory early discovery
30%
success rate

Lead identification
65%
success rate

Lead optimization
55%
success rate

Preclinical transition
55%
success rate

Phase I
70%
success rate

Phase II
50%
success rate

Phase III
65%
success rate

Registration
95%
success rate

Basic science

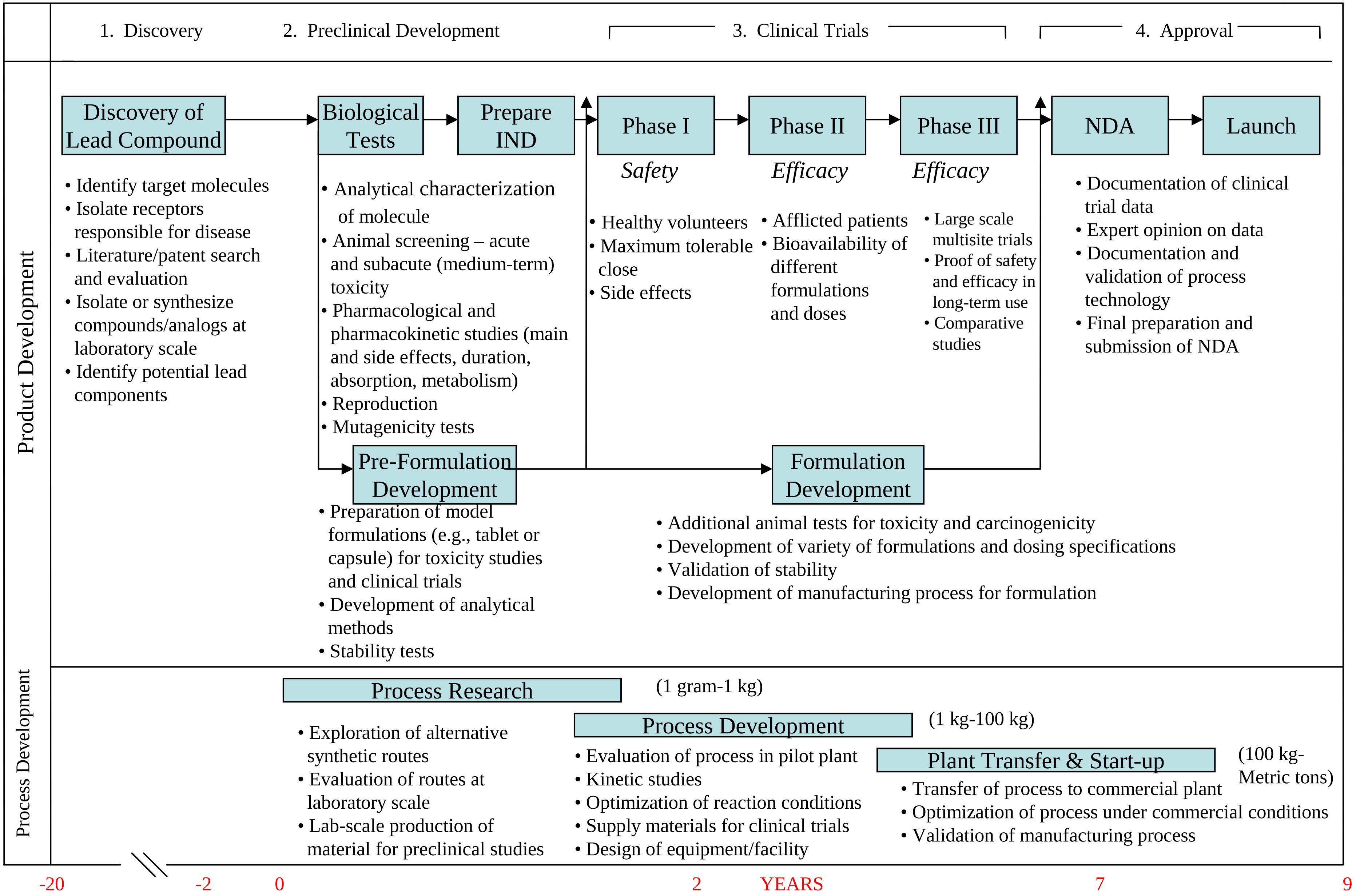
Discovery

Development

Regulatory

From Nature Reviews 2:919, 2003

Time Line for Discovery and Development



1. Discovery
2. Preclinical Development
3. Clinical Trials
4. Approval

Product Development

Discovery of Lead Compound

- Identify target molecules
- Isolate receptors responsible for disease
- Literature/patent search and evaluation
- Isolate or synthesize compounds/analogs at laboratory scale
- Identify potential lead components

Biological Tests

- Analytical characterization of molecule
- Animal screening – acute and subacute (medium-term) toxicity
- Pharmacological and pharmacokinetic studies (main and side effects, duration, absorption, metabolism)
- Reproduction
- Mutagenicity tests

Prepare IND

Phase I

Safety

- Healthy volunteers
- Maximum tolerable close
- Side effects

Phase II

Efficacy

- Afflicted patients
- Bioavailability of different formulations and doses

Phase III

Efficacy

- Large scale multisite trials
- Proof of safety and efficacy in long-term use
- Comparative studies

NDA

Launch

- Documentation of clinical trial data
- Expert opinion on data
- Documentation and validation of process technology
- Final preparation and submission of NDA

Pre-Formulation Development

- Preparation of model formulations (e.g., tablet or capsule) for toxicity studies and clinical trials
- Development of analytical methods
- Stability tests

Formulation Development

- Additional animal tests for toxicity and carcinogenicity
- Development of variety of formulations and dosing specifications
- Validation of stability
- Development of manufacturing process for formulation

Process Development

Process Research (1 gram-1 kg)

- Exploration of alternative synthetic routes
- Evaluation of routes at laboratory scale
- Lab-scale production of material for preclinical studies

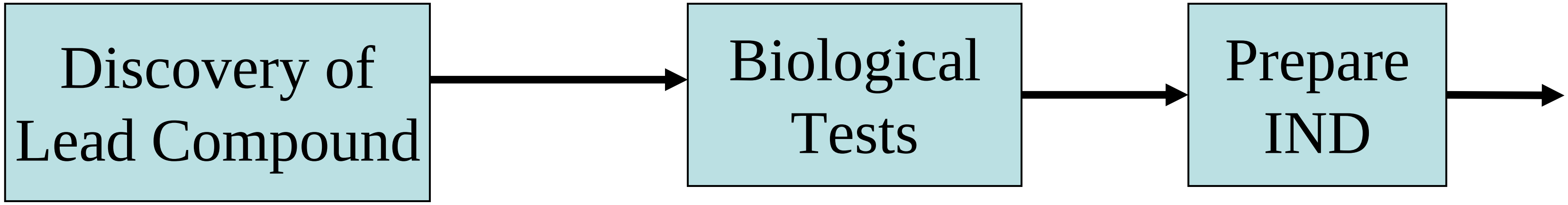
Process Development (1 kg-100 kg)

- Evaluation of process in pilot plant
- Kinetic studies
- Optimization of reaction conditions
- Supply materials for clinical trials
- Design of equipment/facility

Plant Transfer & Start-up (100 kg-Metric tons)

- Transfer of process to commercial plant
- Optimization of process under commercial conditions
- Validation of manufacturing process

Discovery & Preclinical Development



Discovery of Lead Compound

Biological Tests

Prepare IND

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Clinical Trials

Phase I

Safety

- Healthy volunteers
- Maximum tolerable dose
- Side effects

Phase II

Efficacy

- Afflicted patients
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- Large scale multisite trials
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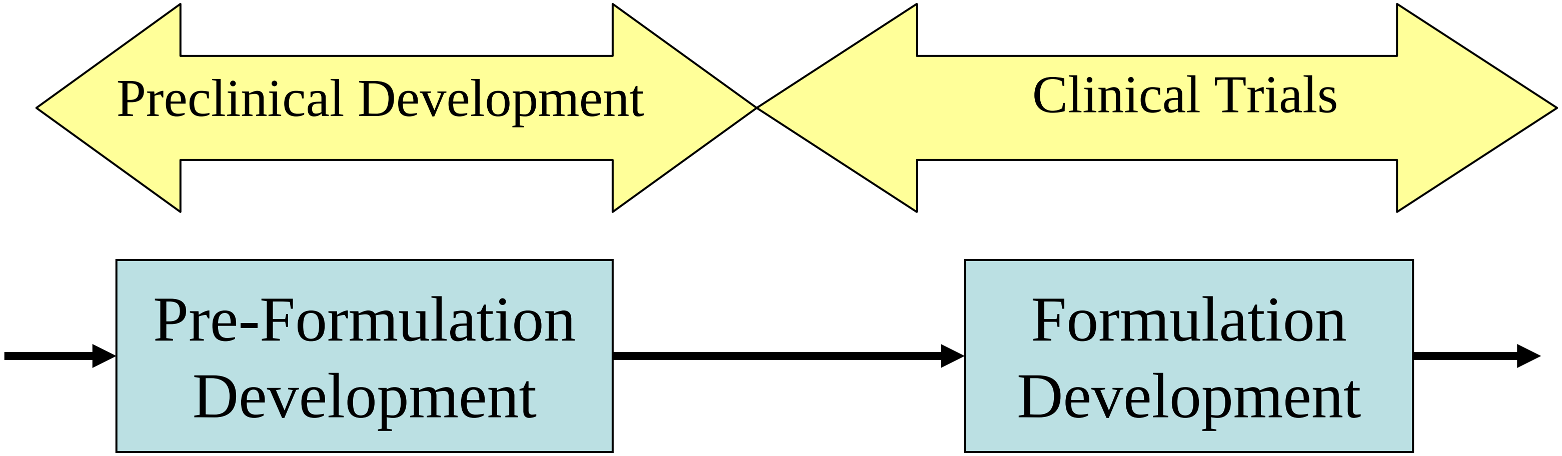
Formulation Design



Preclinical Development

Clinical Trials

Pre-Formulation Development

Formulation Development

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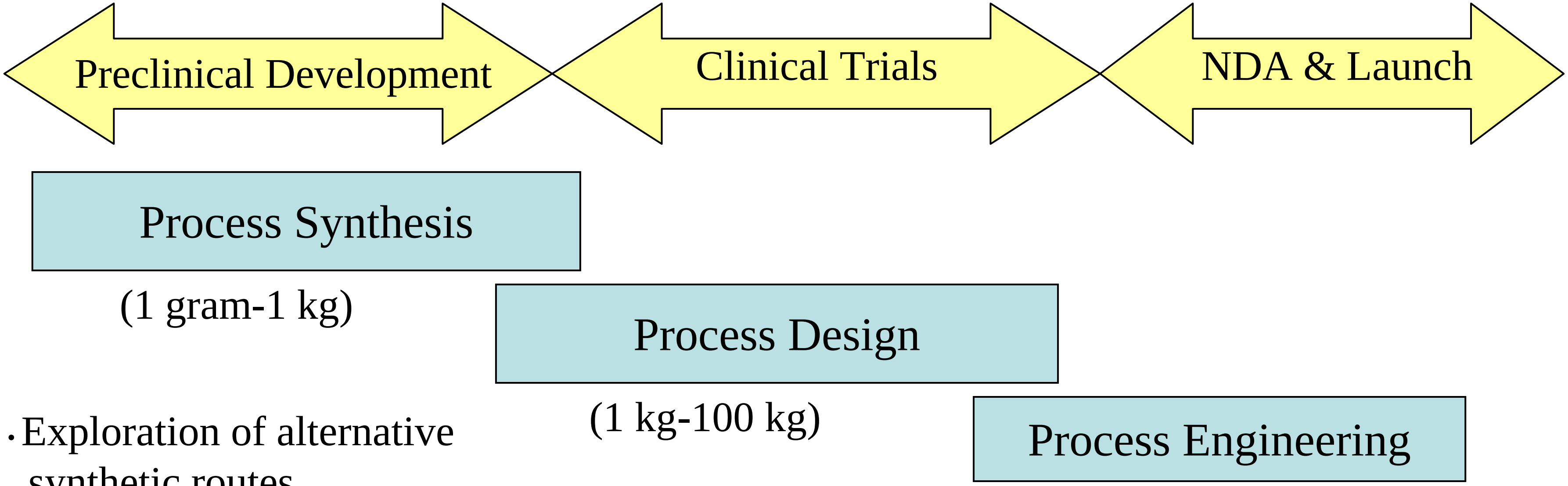
Process Design & Development



Preclinical Development

Clinical Trials

NDA & Launch

Process Synthesis

(1 gram-1 kg)

- Exploration of alternative synthetic routes
- Evaluation of routes at laboratory scale
- Lab-scale production of material for preclinical studies

Process Design

(1 kg-100 kg)

- Evaluation of process in pilot plant
- Kinetic studies
- Optimization of reaction conditions
- Supply materials for clinical trials
- Design of equipment/facility

Process Engineering

(100 kg- metric tons)

- Transfer of process to commercial plant
- Optimization of process under commercial conditions
- Validation of manufacturing process

Challenges of Pharma Product Development

Discovery

Development

Launch

$

9-13 years

$600 - $1.200 Million

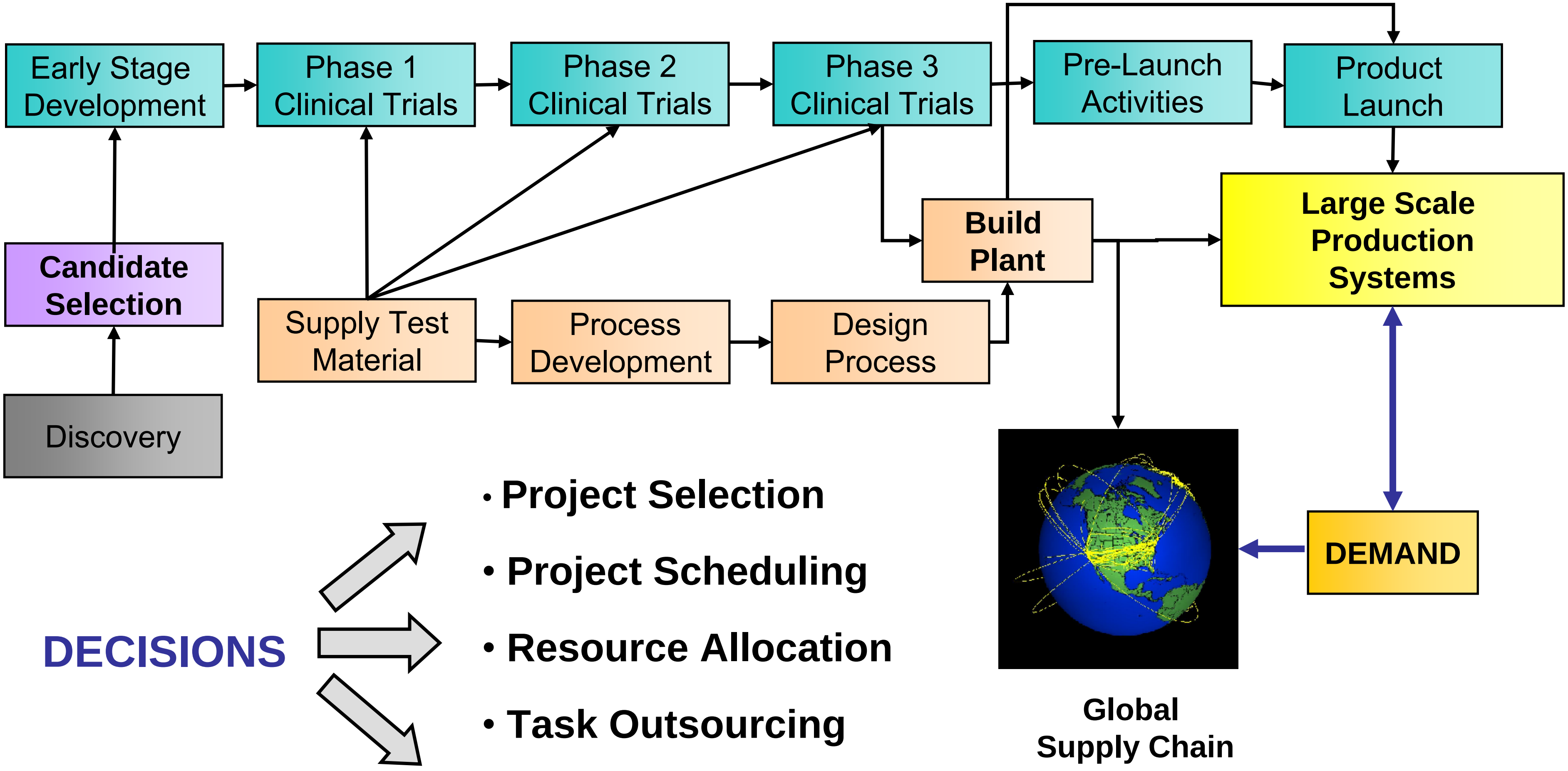
Many Project Candidates

- In-House discoveries
- In-Licensed products
- Line-extensions

Development Process features

- Long duration & high development cost
- Many task & variety of resources
- High degree of technical uncertainty
- High degree of market uncertainty
- Dependencies among candidates
- Regulatory requirements/limitations

Pharmaceutical Product Development (PPD) Activity Network



Early Stage Development

Phase 1 Clinical Trials

Phase 2 Clinical Trials

Phase 3 Clinical Trials

Pre-Launch Activities

Product Launch

Candidate Selection

Discovery

Supply Test Material

Process Development

Design Process

Build Plant

Large Scale Production Systems

DEMAND

Global Supply Chain

DECISIONS

- **Project Selection**
- **Project Scheduling**
- **Resource Allocation**
- **Task Outsourcing**
- **Project Termination**

Uncertainties

- Technical
  - Failure of preclinical tests & clinical trials
  - Failure in Phase IV (post-launch)
  - Duration of development tasks
  - Resource requirements of tasks
  - Manufacturing facility capital cost
- Market uncertainties
  - Sales level & price
  - Resource availability & costs
  - Competitors' actions
- Internal dependencies

Internal Dependencies

- ❑ Resource Dependency.
  - ➢ Experiments sharing resource personnel.
  - ➢ Learning curve effect resulting in reduced development time for a trailing product of two similar product types

- ❑ Manufacturing Dependency
  - ➢ Learning curve for similar products results in reduced capital cost of facilities for trailing product

- ❑ Financial Return Dependency.
  - ➢ Cannibalization occurs with substitute products
  - ➢ Synergies occur with complimentary products

- ❑ Technical Dependency
  - ➢ Two similar drugs in pipeline, success of one can significantly enhance the success of other drug

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Valuation

- Is the process of determining the worth of an asset or company using a combination of objective and <u>subjective</u> tools .
- The worth in an uncertain environment depends on the balance between reward (value creation) and risk

Expected Net Present Value (ENPV)

- Present value (PV)
- Net Present Value (NPV)
- Expected Net Present Value
  - Multiple scenarios
  - Probability-weighted sum of NPV
- Key Limitation: Discounting factor reflects both time value of money & risk level of investment decision

Risk

- The quantifiable likelihood of loss or less-than-expected returns resulting from uncertainty
- Types of uncertainty:
  - External:
    - Demand of products
    - Supply of raw materials
    - Exchange rates
    - Inflation
  - Internal:
    - Time duration and resource requirements
    - Success/Failure prospects

Risk metrics and implications

- Risk metrics:
  - Volatility Measures (finance): deviation from ENPV
    - Variance
    - Semi-variance
  - Probability of losing money (negative ENPV)
  - Mean loss
- Limitations of the current approaches
  - Constant discounting factor → Risky projects are overestimated, safe projects are underestimated
  - No inclusion of hedging tools (financial and real options) → Iterative refinement of decisions to reduce risk and increase rewards
- In ENPV valuation model higher risk is reflected in higher discounting factors

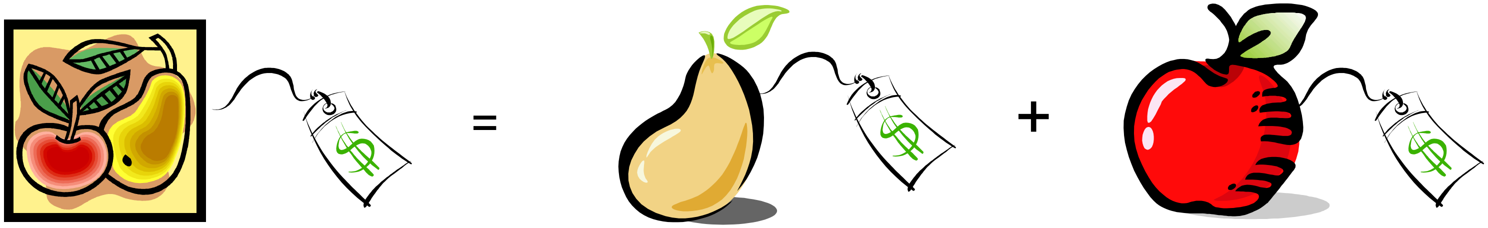
Real Options Valuation (ROV)

- Discount cash flow (DCF)
  - ENPV uses a fixed discounting factor
  - No decision-making flexibilities and its impact in the value of the project are considered

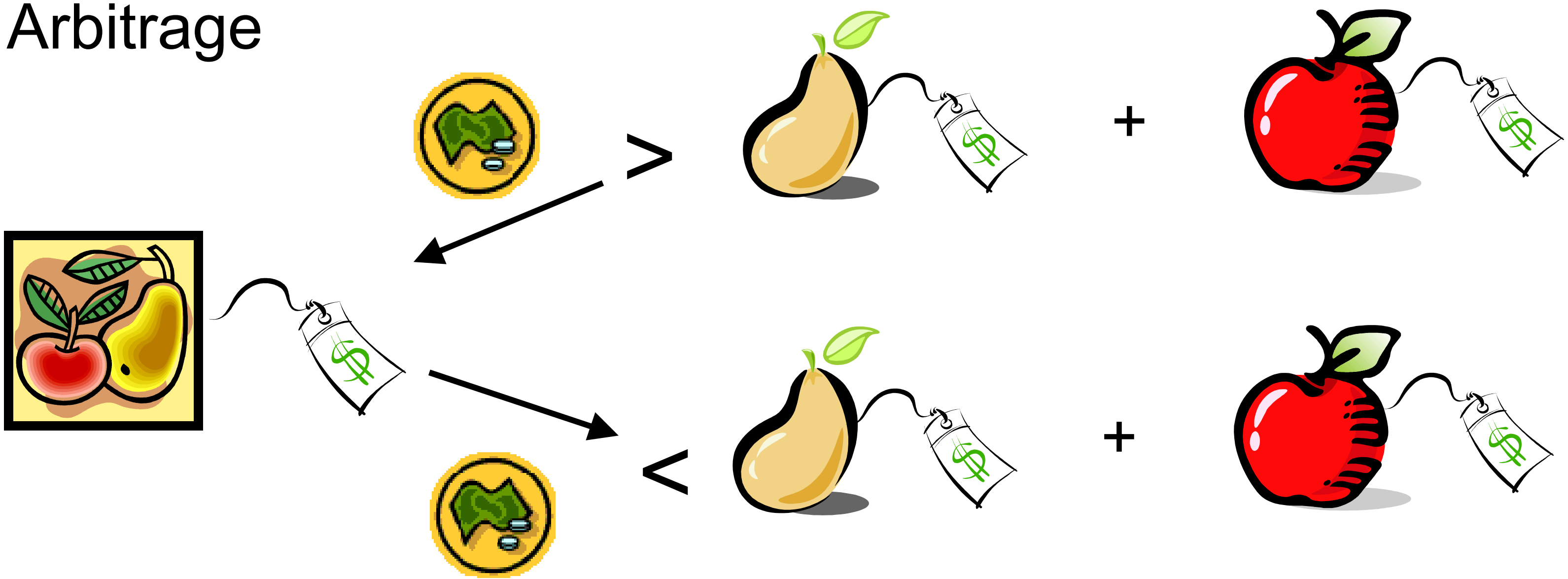
- ROV
  - No arbitrage principle
    - Riskless (perfectly hedged) portfolio has to have a return no different than the risk free asset (e.g. T-bill)
  - Risk depends on state of system, context, and choices/flexibilities available

No arbitrage principle

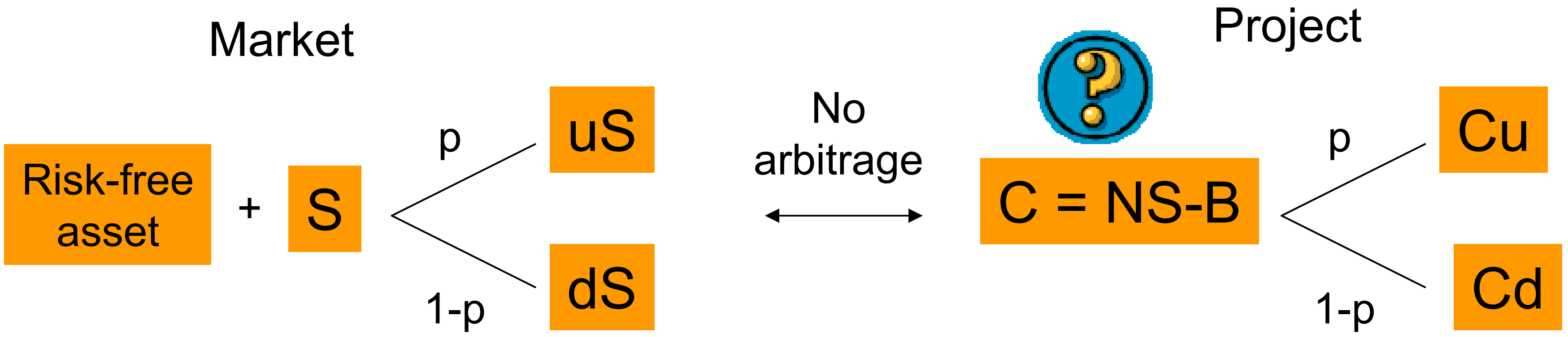
No arbitrage



Arbitrage



No arbitrage principle



S = current risky asset price
C = current project price
N = # of shares of risky asset
B = $ borrowed at the risk free rate
u, d = 1 + % up and down

$$N(uS)-(1+r_f)B=Cu$$

$$N(dS)-(1+r_f)B=Cd$$

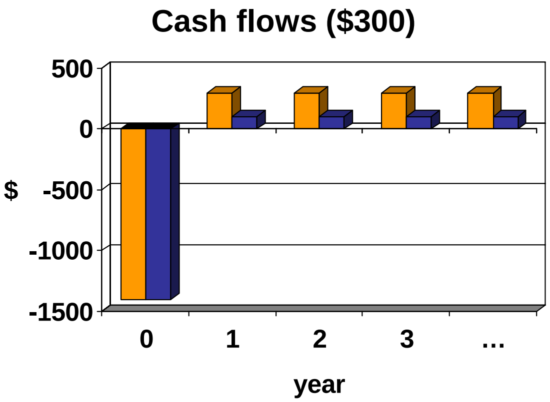
solving ↓

$$C=NS-B=\frac{1}{1+r_f}\left[qCu+(1-q)Cd\right]$$

where

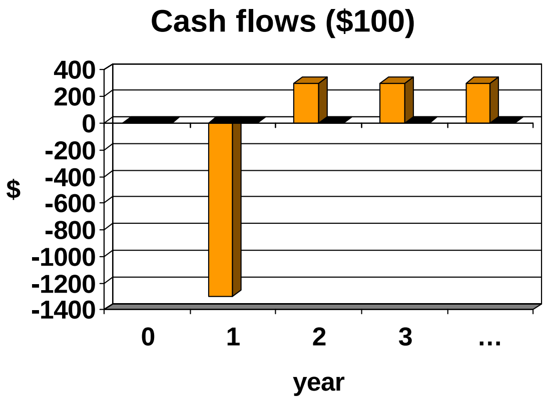
$$q=\frac{1+r_f-d}{u-d}$$

Why do we want to capture flexibility?



Cash flows ($300)

or



Cash flows ($100)

Invest now

$$NPV = -1600 + \sum_{t=0}^{\infty} \frac{200}{(1.1)^t} = -1600 + 2200 = 600$$

Differ

$$NPV = 0.5 Max\left[\frac{-1600}{1.1} + \sum_{t=1}^{\infty} \frac{300}{(1.1)^t} \text{ , } 0 \right] + 0.5 Max\left[\frac{-1600}{1.1} + \sum_{t=1}^{\infty} \frac{100}{(1.1)^t} \text{ , } 0 \right]$$

$$NPV = 0.5\left[\frac{1700}{1.1} \right] + 0.5[0] = 773$$

Options Concepts

- Option: right but not obligation to buy/sell asset at future date at predetermined price
  - Underlying asset = security delivered when option exercised
  - Date = expiration date
  - Predetermined price = strike price
  - Volatility = measure of fluctuation of return on asset
  - Risk-free return = return of asset with fixed rate (i.e. T-bill)
  - Value of option = premium ↔ insurance policy price

- Types
  - Call option = right to buy
  - Put option= right to sell

- Categories
  - American option = exercised any time prior to expiration date
  - European option = exercised only on experation date

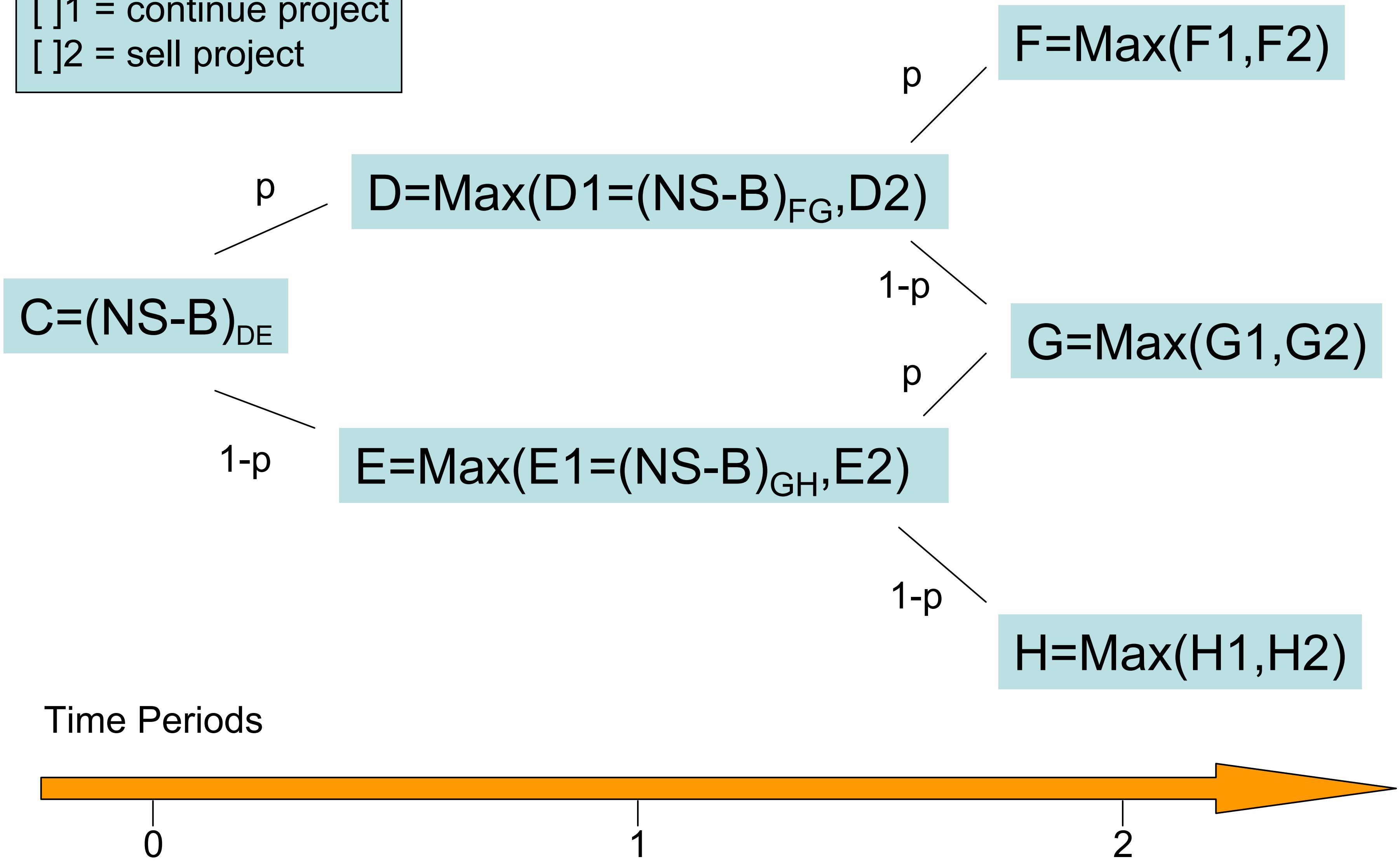
Call & put options

- Put option:
  - You feel that this year's harvest will be good
  - You propose deal to Applejuice.Inc (AI): you pay them \$x now if they guarantee buying price of \$y per ton (T).
  - Spot price when the harvest is due: \$z
    - If z > y → you do not exercise option → you lose \$x; AI saves \$x
    - If z < y → you exercise option → you make an additional \$(y-z)*T-x and AI loses that amount

- Call option:
  - AI forecasts a bad harvest
  - AI proposes deal: AI pays you \$x now if you guarantee selling price of \$y per ton (T)
  - Spot price when the harvest is due: \$z
    - If z > y → AI exercises option → you lose \$(z-y)*T-x; AI saves that amount
    - If z < y → AI does not exercise option → you make an additional \$x; AI loses \$x.

ROV

[ ]1 = continue project
[ ]2 = sell project



$F=Max(F1,F2)$

p

p

$D=Max(D1=(NS-B)_{FG},D2)$

1-p

$C=(NS-B)_{DE}$

$G=Max(G1,G2)$

p

1-p

$E=Max(E1=(NS-B)_{GH},E2)$

1-p

$H=Max(H1,H2)$

Time Periods

DCF and ROV Summarized

DFC rule: $Max_{(at\ \ t=0)}\left[0, E_0\left\{V_T - X\right\}\right]$

ROV rule: $E_0\left\{Max_{(at\ \ t=T)}\left[0, V_T - X\right]\right\}$

Nomenclature:

E_0 Expectation in present value

V_T Future positive cash flow

X Cost of exercising the option

Summary

- PPD management = stochastic decision problem with high risk & high payoff
- PPD Pipeline involves network of tasks, many following fixed task precedence relationships
- Key decisions elements:
  - Selection of projects & termination of projects
  - Sequencing, scheduling, resource assignments
  - Selection of hedging strategies
- Key complicating issues: failure / termination of projects
- Conventional approaches
  - Use ENPV & Risk measures with implicit parameterization of risk embedded in discount factor
  - Single objective with risk constraint or two objective optimization
- Real options valuation can capture true flexibility of multistage decision process & dynamics of risk

Solution Approaches to be Reviewed

Multi-stage Decision Problem under Uncertainty

- Stochastic Mathematical Programming
  - Project selection/termination
  - Resource constrained scheduling
  - Risk vs Return trade-offs
  - Valuation of flexibility
- Discrete Event Simulation
  - Modeling of uncertainties
  - Decision making: project selection & scheduling aspects
- Hybrid Strategy – SIMOPT
  - Heuristic Decomposition Approach

Mathematical Programming Approaches

- Literature overview
- Resource overbooking model:
  Honkomp et al(1999)
- Resource-constrained Test Scheduling:
  Jain & Grossmann (1999)
- Real Option-based Portfolio model
  Rogers et al (2002)
- Summary

PPD Management Problem

Given Set of Candidate Products:

  - Each product has (partial) precedence network of tasks
  - Common pool of limited resources of various kinds
  - Task outsourcing possibilities
  - Performance measure

- Determine subset of products to pursue
- Assign resources to development tasks
- Optimize performance measure

Practical complications:

- Uncertainties in
  - Task Processing Duration
  - Task Resource Requirements & Availability
  - Task Success/Failure Probability
  - Task Costs & Product Revenue
- Synchronization of internal & in-licensed candidates

Result: Stochastic Optimization Problem

Math Program Literature with Stochastic Elements

- Honkomp , Pekny & Reklaitis (1999)
  - Select products from portfolio of candidates
  - Resource constraints satisfied in expected value (overbooking)
- Smith & Grossmann (1996)
  - Fixed set of products with testing tasks with known failure probability
  - Sequencing/scheduling of testing tasks under unlimited resources
- Jain & Grossmann (1999)
  - Constrained resources
  - Include option of outsourcing tests
- Maravelias & Grossmann (2004)
  - Installation/acquisition of additional resources
  - Resource allocation mode: task duration linear function of resource level
  - Improvements in solution methodology
- Rogers, Gupta & Maranas (2002)
  - Real option based portfolio selection model
  - Single resource: ($ budget)
- Rogers, Maranas & Ding(2005)
  - Extension to In-Licensing
  - Investment timing & policies
- Levis & Papageorgiou (2004)
  - Product selection & capacity planning
  - Aggregated development pipeline (lumped product success probability)
  - Capacity planning & siting under demand uncertainty

Overbooking Formulation

(Honkomp et al 1999; Subramanian et al 2001)

Objective: Select projects to maximize expected NPV

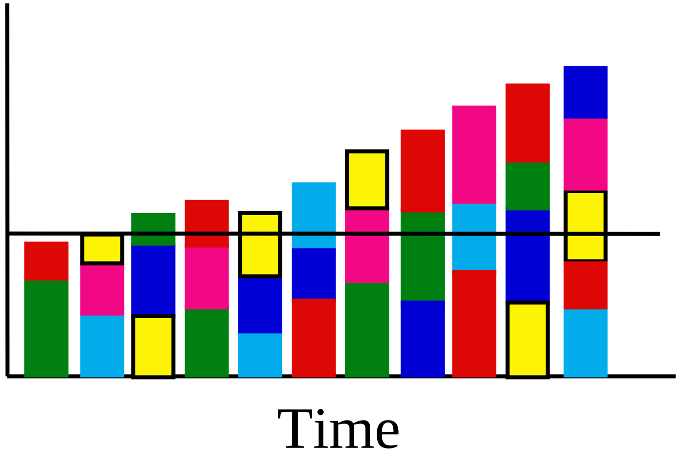
Specific Problem Features:

- Projects defined by network of development tasks with specified task durations, requirements for each resource, probability of failure
- Each project has due date
- When a project task fails, project is terminated
- Constrained resources

Problem formulation: Discrete time MILP

Key construction: Overbooking

Formulate resource constraints
by weighting resource requirements
by probability of task success



Formulation Variables

Uniform time discretization formulation

Binary:

$X_{it} = 1$ if task *i* is started at time *t* and *0* otherwise

- **O**(tasks *x* time periods)

Continuous:

$S_{r,t}$ = Amount of available resource *r* left unused at time *t.*

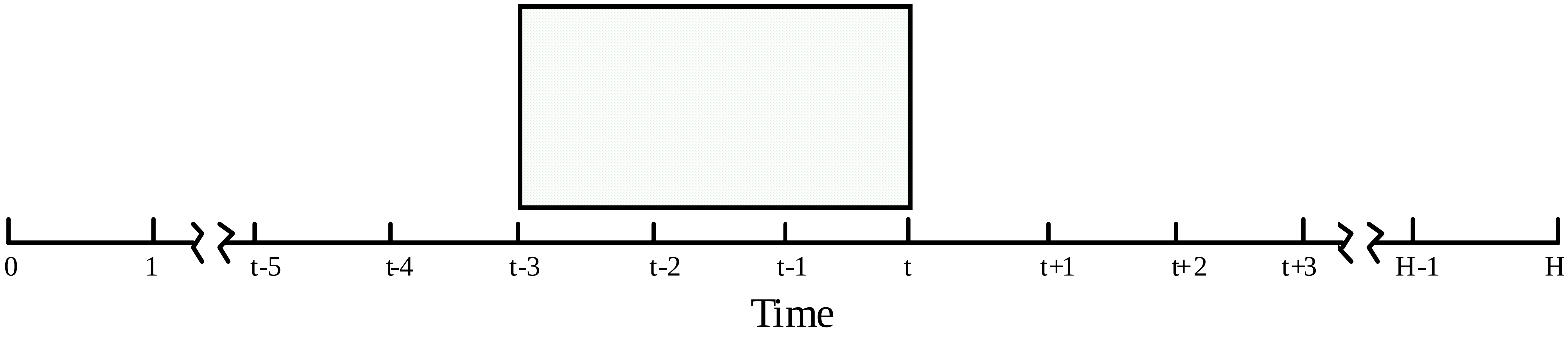
- **O**(resources *x* time periods)

$H_{i,i',t}$ = Variable to allow task i following task i' at time t to wait before starting

- **O**((tasks)^2 *x* time periods)

Allocation Constraints

Permit task to occur only once during planning horizon, H.



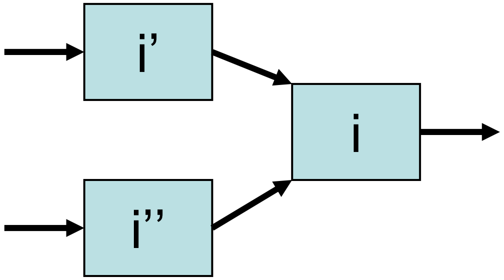
$$\sum_{t=1}^{H-p_{it}} X_{it} \leq 1 \quad \forall i$$

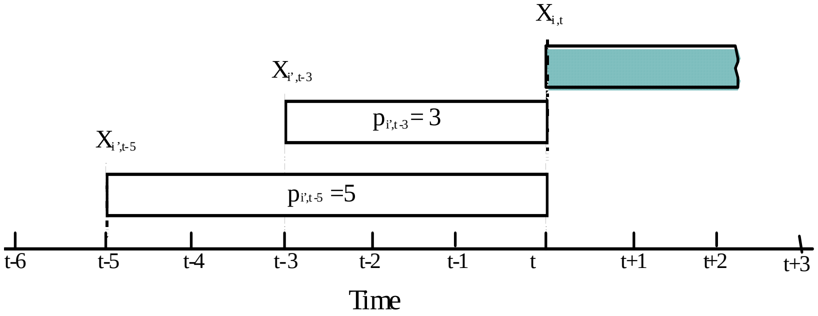
p_{it} = processing time of task i at start of time t

# of Constraints **O**(tasks)

Precedence Constraints

Enforce requirement that predecessor tasks be completed before successor task is started





$$H_{i,i',t} = H_{i,i',t-1} + \sum_{t' \mid t' + p_{i't'} = t} X_{i',t'} - X_{it} \quad \forall i \in AND_{in}, i' \in T_{bi}^{I}, 1 \le t \le H - p_{it}$$

and $0 \le H_{ii't} \le 1$ $\quad 1 \le t \le H$

AND_{in} = set of tasks with in-tree structure & AND connectivity

T_{bi}^{I} = set of tasks immediately preceding task i

# of Constraints 2x **O**((tasks)^2 x time periods)

Demand Constraints

Requires that tasks with specified demands be started prior to time of demand.

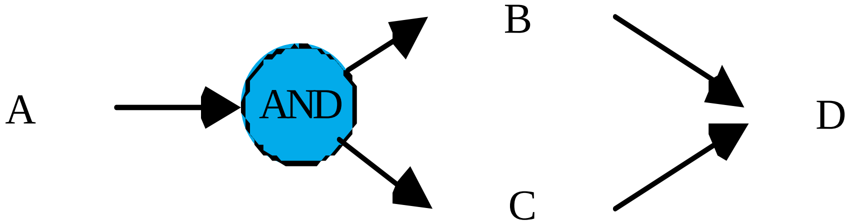
$$\sum_{t=1}^{d \;\; - p_{it}} X_{it} = 1 \qquad \forall i \in \{T_h\}$$

Similar constraints for task with demand times which can be violated with penalty

# of Constraints **O**(tasks)

Task Probabilities

For serial & branched cases, ALL tasks prior to the current task must complete successfully.



T_{bi} = set of all tasks preceding task i

$$P_i^S = \prod_{i' \in T_{bi}} \pi_{i'} \quad \forall i$$

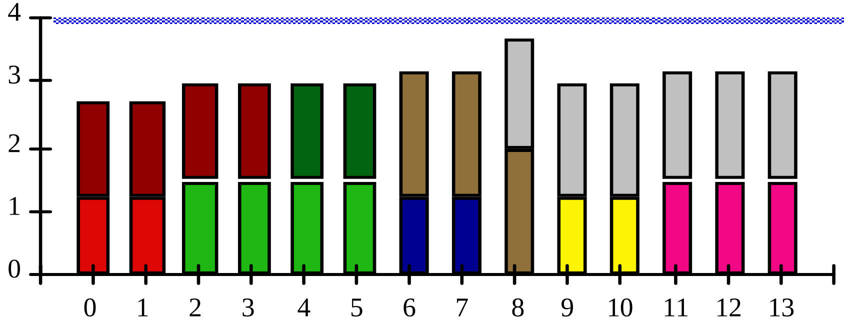
Cumulative probability for task i starting (relevant for resource consumption)

$$P_i^F = \prod_{i' \in T_{bi} \cup \{i\}} \pi_{i'} \quad \forall i$$

Cumulative probability for task i finishing (relevant for project return)

Resource Constraints

Expected utilization of renewable resources at any time can not exceed availability



$$\sum_{i=1}^{Ntasks} \sum_{t'=0}^{p_{it}-1} P^{S}_{it-t'} r_{i,t-t',t',r} X_{it-t'} + S_{rt} = U_{rt} \quad \forall r,t$$

# of Constraints **O**(resources x time periods)

Objective Function

Expected NPV = Exp {Reward – costs - penalties}

Expected Reward: $$+\sum_{t=E_i}^{L_i} P_{it}^{F} C_{it}^{D} X_{it} \quad \forall i$$

Expected Cost: $$-\sum_{t=E_i}^{L_i} P_{it}^{S} C_{it}^{E} X_{it} \quad \forall i$$

O(tasks *x* time periods)

Late Completion Penalty: $$-\sum_{t=d_i}^{L_i} P_{it}^{F} \left(C_i^{F} + (t-d_i) C_i^{V} \right) X_{it} \quad \forall i \in \{T_s, T_f\}$$

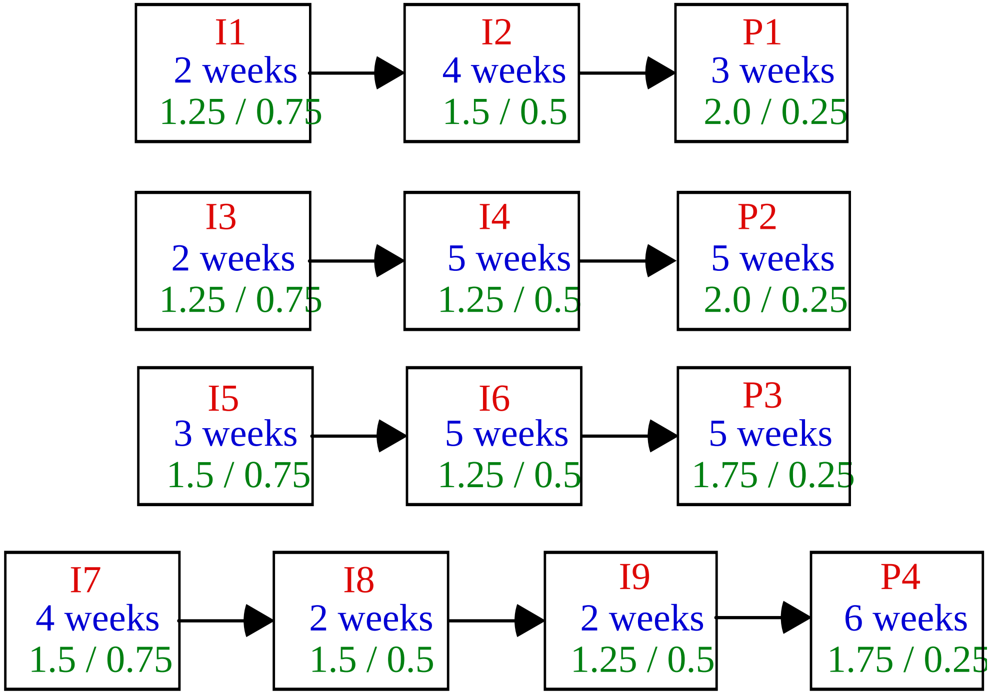
Under Utilized Resource: $$-\sum_{t=1}^{H-1} C_{rt}^{S} S_{rt} \quad \forall r$$

O(resources *x* time periods)

Example

Problem Parameters

- Four Projects: values 3,2,1,4
- Resources: A (max 4), B(max 2)
- Penalty for idle resources
- Conditional probability of task success: 1st task 0.7; last 0.5; others 0.6
- Due dates: 7, 12, 13, 14
- Additional 16 lower priority supporting tasks
- Maximize expected return over horizon of 14 weeks



I1
2 weeks
1.25 / 0.75

I2
4 weeks
1.5 / 0.5

P1
3 weeks
2.0 / 0.25

I3
2 weeks
1.25 / 0.75

I4
5 weeks
1.25 / 0.5

P2
5 weeks
2.0 / 0.25

I5
3 weeks
1.5 / 0.75

I6
5 weeks
1.25 / 0.5

P3
5 weeks
1.75 / 0.25

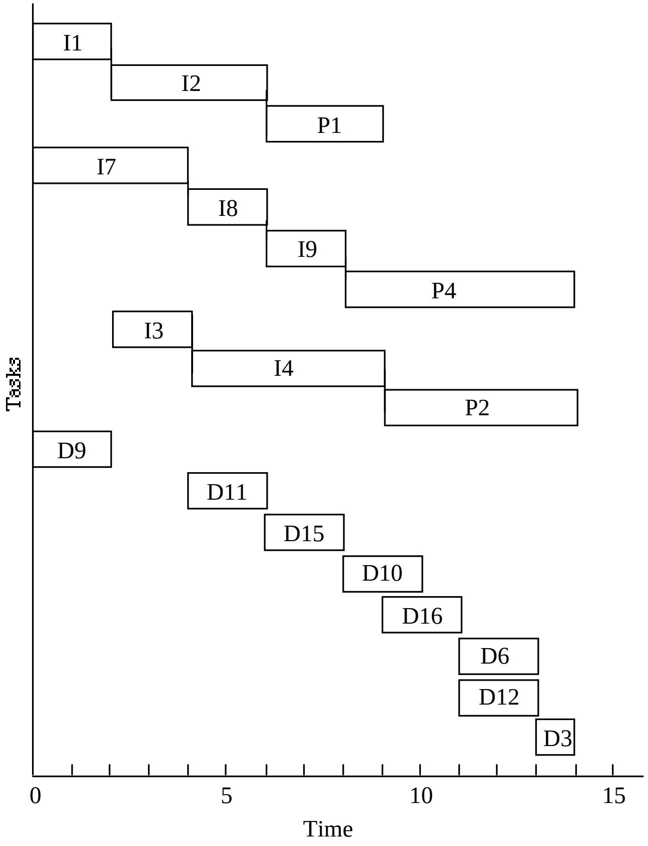
I7
4 weeks
1.5 / 0.75

I8
2 weeks
1.5 / 0.5

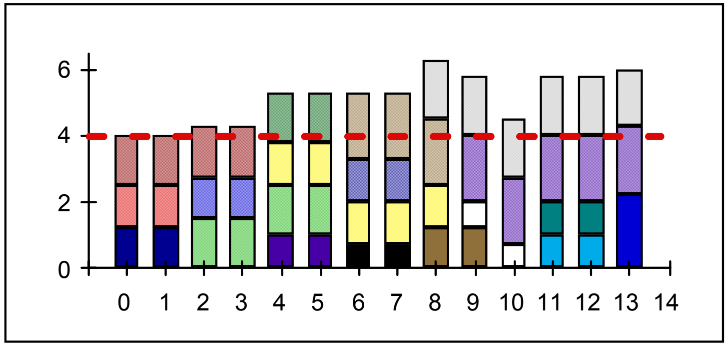
I9
2 weeks
1.25 / 0.5

P4
6 weeks
1.75 / 0.25

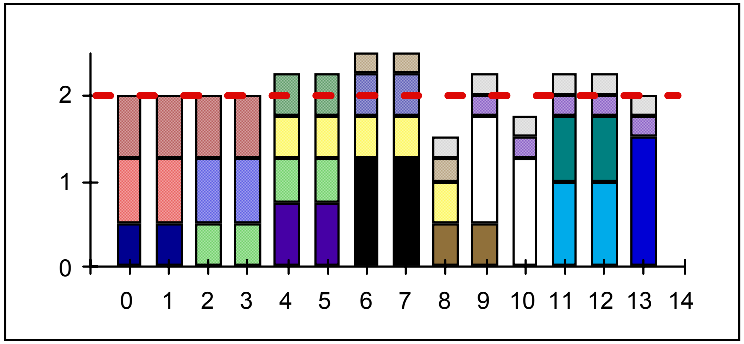
Results for Example



Scheduled Utilization



Resource A



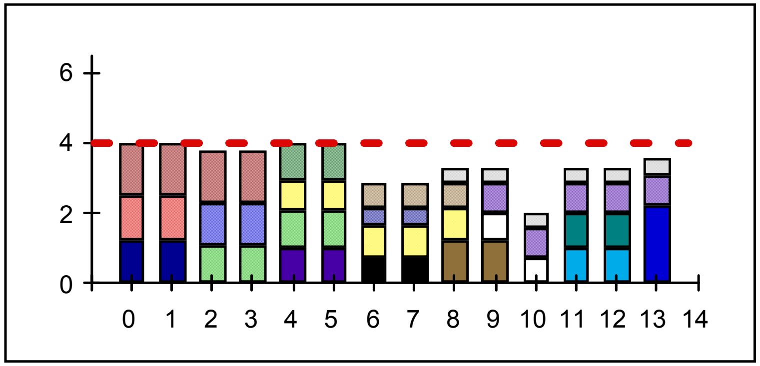
Resource B

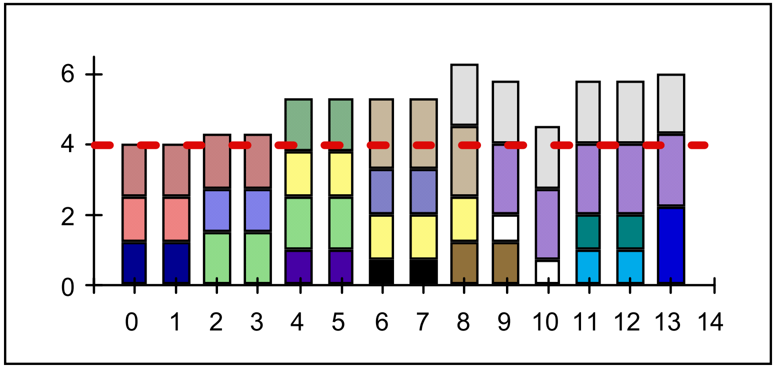
Resource Utilization Profiles

Expected

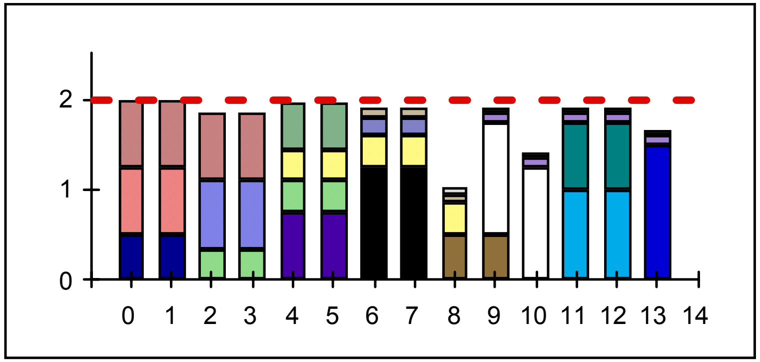
Scheduled

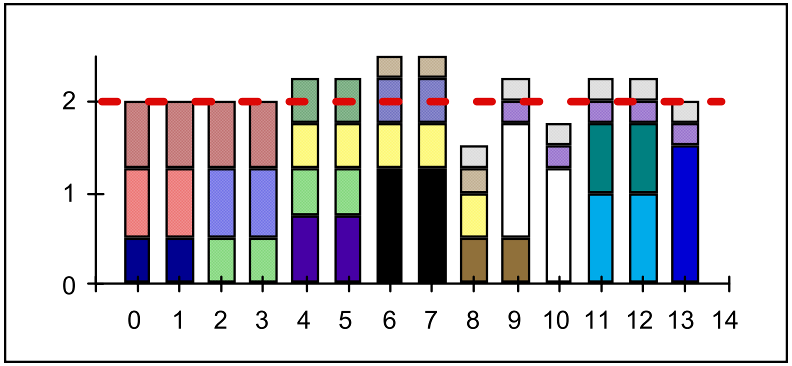
A



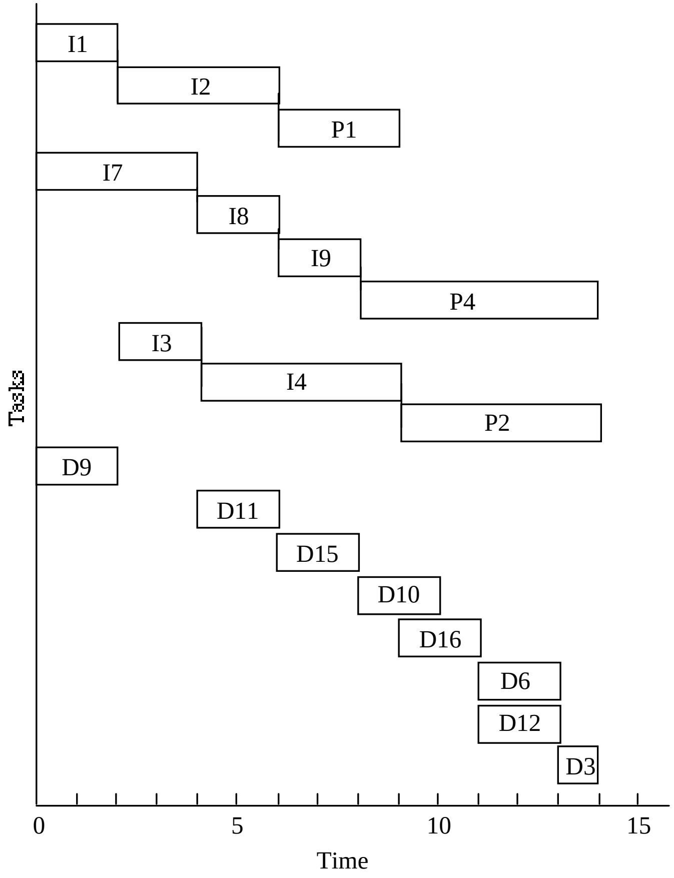


B

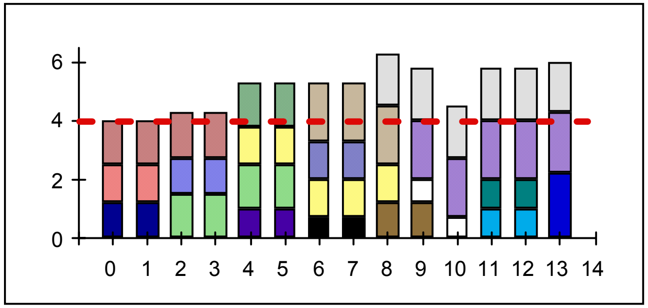




Consequence of Expected Value Approach to Resource Constraints



Scheduled Utilization



Resource A

Solution:
Here & Now project selection

What if all tasks succeed?
What happens if I2 fails?

Extensions & Limitations

- Extensions
  - Bounds on allowed resource overbooking
  - Resource availabilities with multi-level price structure (e.g., overtime)
  - Resource substitution
  - Alternative product development paths
- Limitations
  - Discrete time based formulation caveats
  - Here & now solution: rescheduling needed when resource limit reached
  - No measure of risk

Mathematical Programming Approaches

- Literature overview
- Resource overbooking model:
  Honkomp et al(1999)
- Resource-constrained Test Scheduling:
  Jain & Grossmann (1999)
- Real Option-based Portfolio model
  Rogers et al (2002)
- Summary

Test Scheduling Formulation

(Jain & Grossmann 1999)

Objective: Schedule given products to minimize expected value of testing cost + decrease in commercialization revenue due to delayed testing completion

Specific Problem Features:

- Product selection given a priori
- Test sequencing considered if no precedence constraints imposed
- Outsourcing of test allowed
- Deterministic resource constraint
  - Resource availability & utilization discrete/integer
  - Extra resource needs met via outsourcing

Problem formulations:

Continuous time MILP with time slot based resource constraints

Continuous time MILP with graph-based resource constraints

Key construction: Expected cost of completion of test via disjunction & linear approximation

Variable Sets

Continuous time (slot type) formulation

- Time coordinates (continuous)
  - Time coordinate for tasks: Start time of task i, s_i
  - Time coordinate for resources: Start time of slot k on resource j, S_{jk}
- Binary variables
  - Task sequencing $y_{i'l}$
  - Outsourcing $\hat{z}_i$
  - Assignment of resource j to task i in slot k, x_{ijk}
  - Assignment of resource j to task i, $\hat{x}_{ij}$

Expected Cost of Test Completion

Components:

- Disjunctive form: no outsourcing or outsourcing
- Continuous discounting factor, function of start time s_i
- Probability of test success p_i
- Binary sequencing variables $y_{i'l}$
- Outsourcing variable $\hat{z}_i$

$$\left(\begin{array}{c} \neg \hat{z}_i \\ C_i = c_i e^{-\bar{r} s_i} \prod\limits_{i' \neq i, i' \in I^{L_i}} p_{i'} y_{i'i} \end{array} \right) \vee \left(\begin{array}{c} \hat{z}_i \\ C_i = \bar{c}_i e^{-\bar{r} s_i} \prod\limits_{i' \neq i, i' \in I^{L_i}} p_{i'} y_{i'i} \end{array} \right)$$

Approximation of nonlinear functions

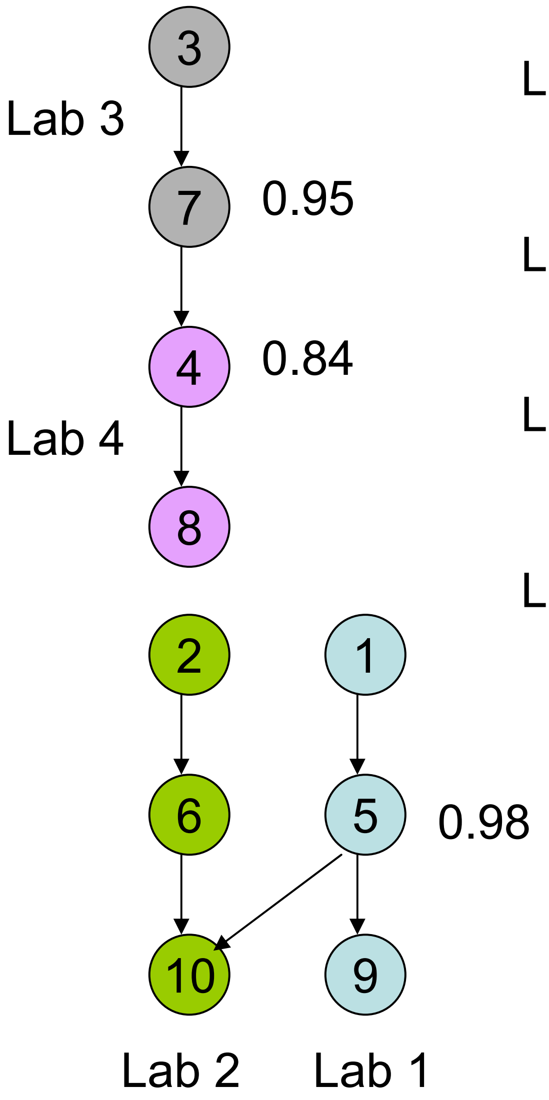
- Exponential transformation
- Piecewise linear approximation
- Convex hull formulation to replace disjunction

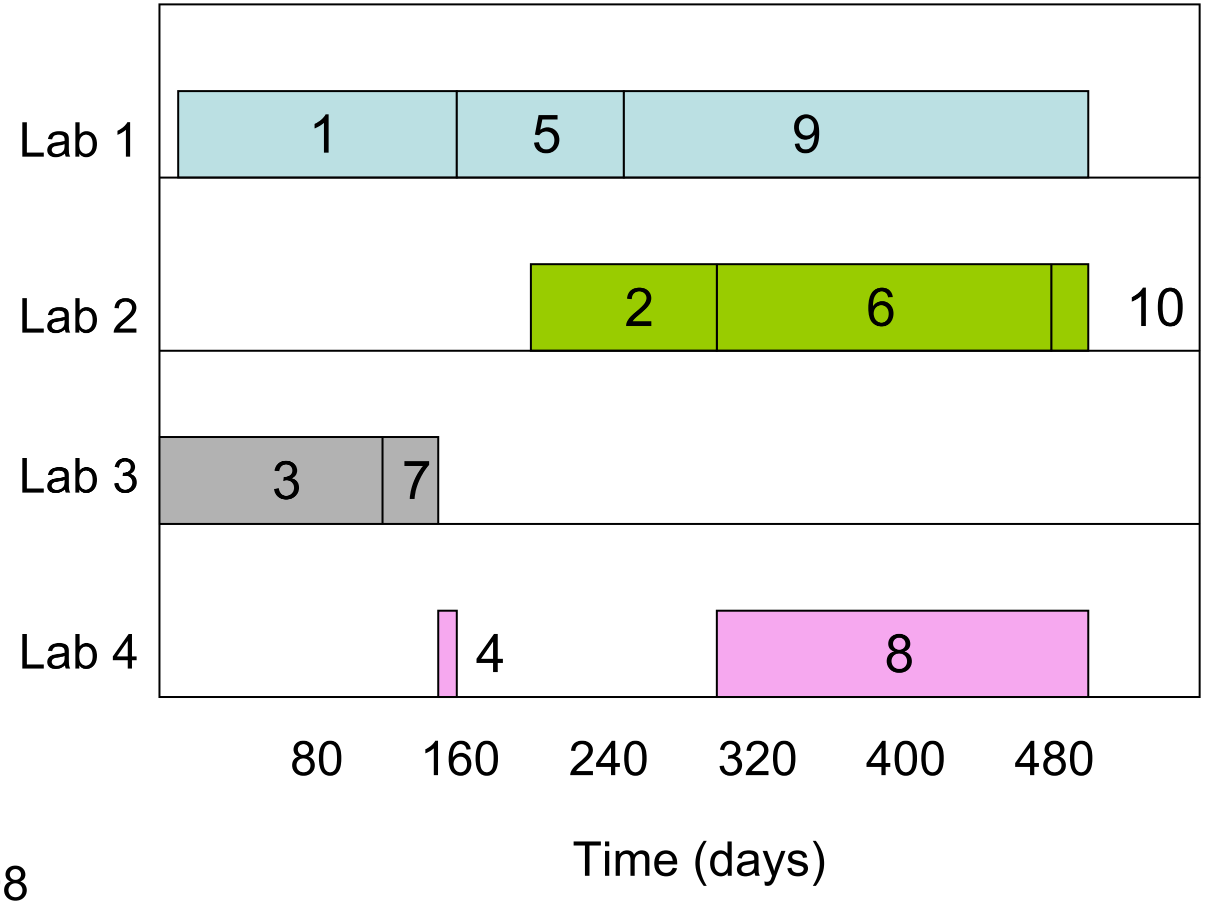
Constraint Sets

- Timing Constraints:
  - Start & completion times of sequential tasks
  - Length of resource slot & task duration*
- Time matching constraints:
  - Synchronization of start of task & start of associated resource slot *
  - Assignment constraints
  - If resource not available, assign to outsource
- Logic cuts
  - Eliminate directed cycles in task sequences
- Logic based resource constraints*
  - Impose constraint to disallow concurrent assignment of same resource to competing tasks of different products

Sample Results

Product 1





No outsourcing used

Model: 108 0-1, 309 cont, 547 constraints
CPLEX 239 nodes, 1.1 CPU s on HP C110

Assessment & Extensions

- Computational Issues
  - Graph based representation of resource constraints improves solution speed (Solved cases with 30 vs. 10 tests)
- Formulation Advantage:
  - If no test fails, solution with outsourcing is feasible
- Formulation Disadvantage:
  - When test fails, solution must be recomputed
  - Project selection decision not addressed
  - Handling of continuous resources (e.g., $ budgets)
- Extensions reported in Maravelias & Grossmann (2004)
  - Installation/acquisition of additional resources
  - Resource allocation mode: task duration linear function of resource level
  - Improvements in solution via preprocessing & decomposition heuristics (Solved case with 3 products, 28 tests)

Mathematical Programming Approaches

- Literature overview
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- Resource-constrained Test Scheduling:
  Jain & Grossmann (1999)
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  Rogers et al (2002)
- Summary

Real Options Based Analysis of PPD

(Rogers, Gupta & Maranas 2002)

Objective : Obtain a decision road map for making optimal project selection decisions according to market conditions

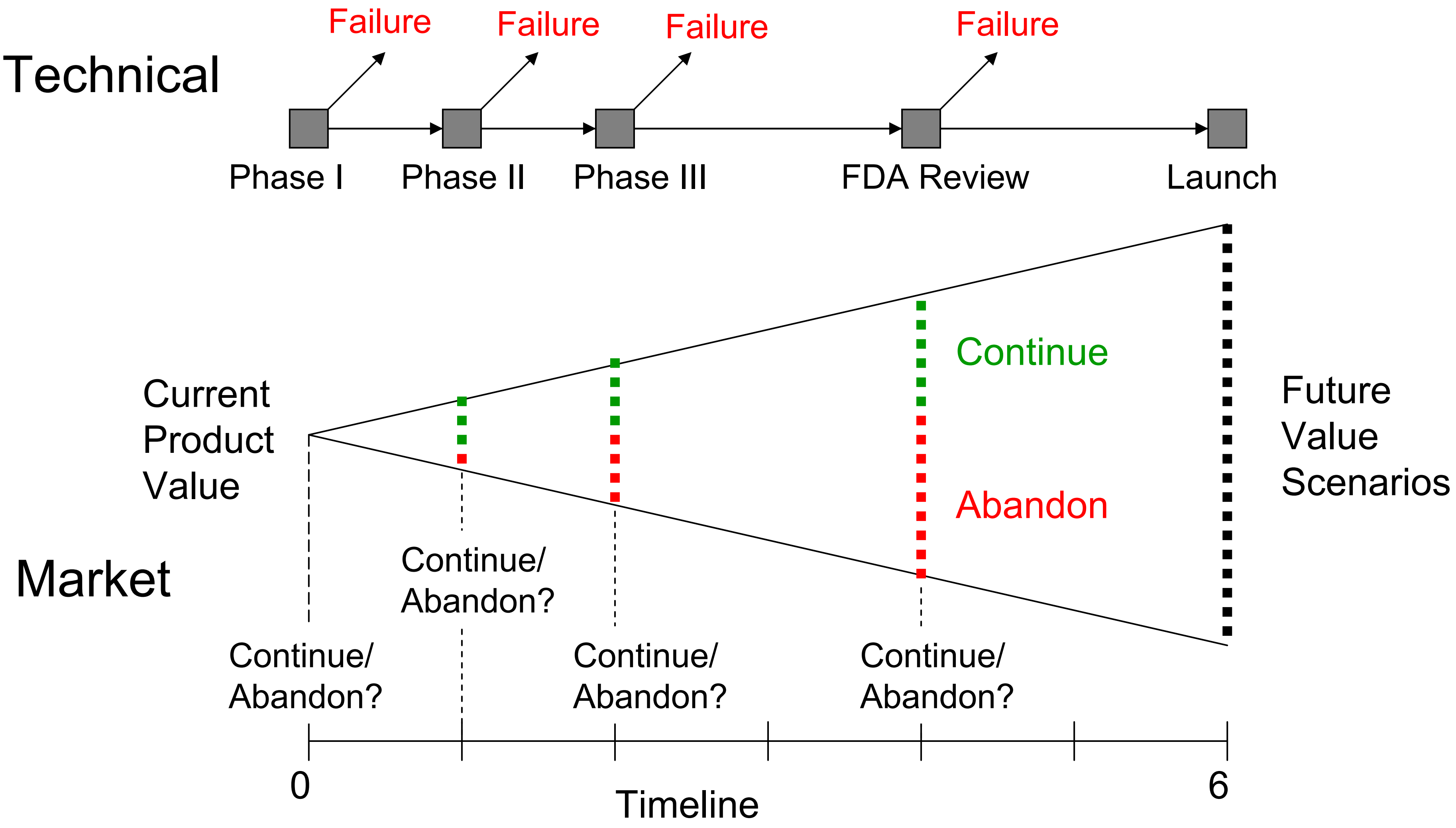
Specific Problem Features:

- Two sources of uncertainty: product market value and technical success/failure
- Market value is modeled as a geometric brownian motion
- Project is abandoned if its ENPV becomes negative
- Abandonment option is modeled as European call option
- Budget constraint (only resource constraint) is based on overbooking approach

Problem formulation: Discrete time MILP

Key construction: Quadranomial multistage decision tree based on market value represented as an MILP through linearization

Product Development Decision under Market & Technical Uncertainty



Formulation

- Key decision variable

  y_{isk_s} =1 if drug I selected to undergo stage s development in value scenario k_s

- Constraints
  - Drug precedence constraints
    - Abandoned drug stays abandoned
  - Value Monotonicity
    - Scenarios ordered in ascending value
  - Resource constraint
    - Overbooking constraint linking drug candidates
  - Real options valuation relations

Real Options Decision Tree Market Value

$$M_{isk_s} = \left[-I_{is} + \frac{\sum_{k_{s+1}=1}^{N_{i,s+1}} \left[\phi_{is}\, p_{ik_s k_{s+1}} M_{i,s+1,k_{s+1}} \right]}{\left(1+r_f\right)^{T_{is}/\Delta T}} \right] y_{isk_s}$$

Market value of product *i* in scenario k_s of stage *s*

Components:

- Probability of technical success ϕ_{is}
- Binary selection variable y_{isk_s}
- Conditional probability of moving from scenario k_s to scenario k_{s+1} $P_{ik_s k_{s+1}}$

Re-formulation devices

Objective Function: Maximize ROV at t=0

$$\sum_i M_{i,s=1,k_{s=1}}$$

Express dependence only
on current & future stage

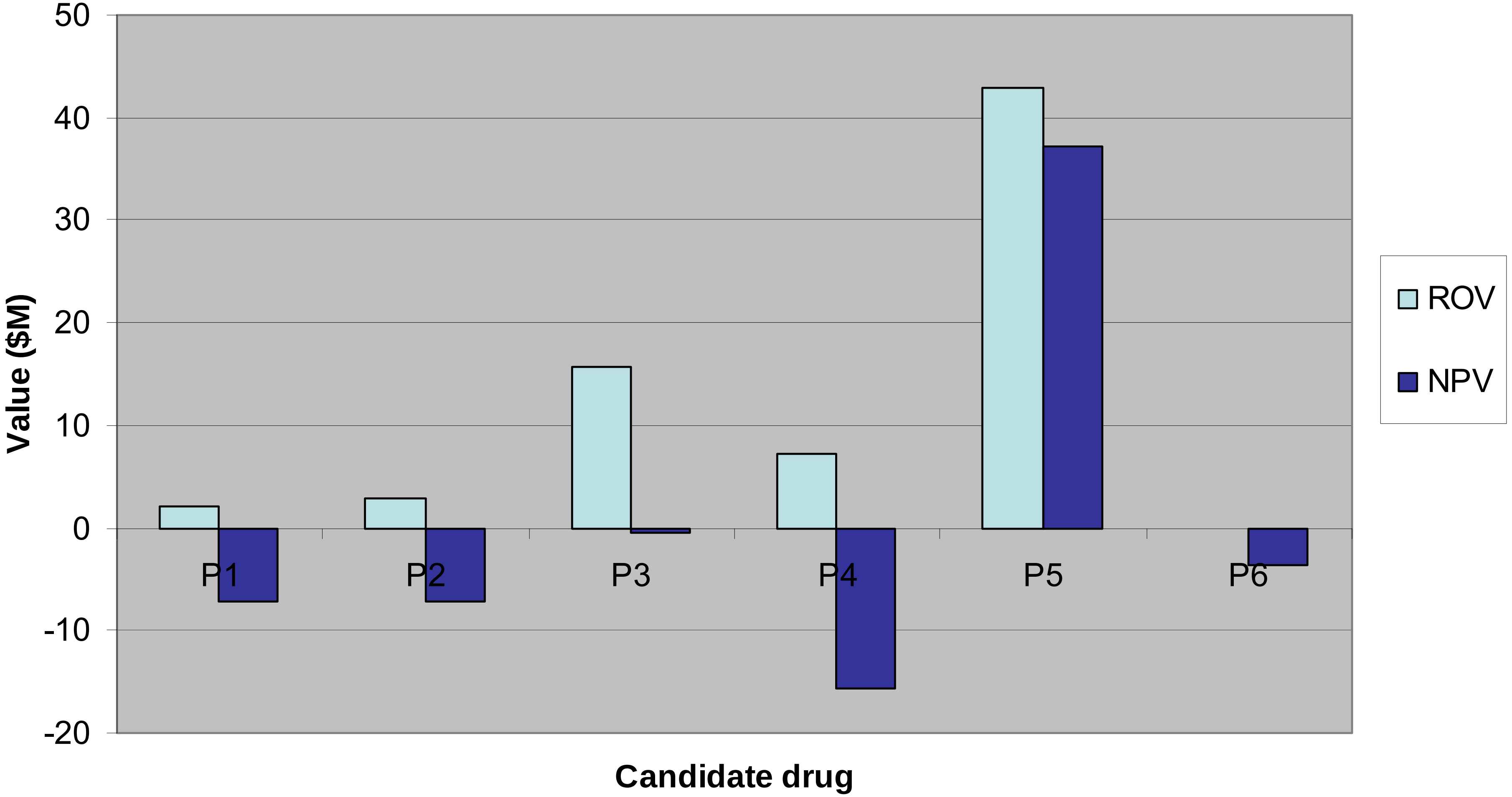
Treatment of continuous-binary pair:

$$M_{isk_s} = \left[-I_{is} + \frac{\sum_{k_{s+1}=1}^{N_{i,s+1}} \left[\phi_{is}\, p_{ik_s k_{s+1}} M_{i,s+1,k_{s+1}} \right]}{\left(1+r_f\right)^{T_{is}/\Delta T}} \right] y_{isk_s}$$

Linearize using added
continuous variable

Linearization requires upper bounds obtained
via solution of problem with no resource constraints

Sample Results



Assessment

- Computational issues: Problem scaling
  - *O* (number of products, stages, scenarios)
- Strength
  - First model-based application of ROV in PPD setting
  - Confirms impact of abandonment option on portfolio valuation
- Limitations
  - Formulation is considerable simplification of reality
    Market model, additional tasks, tests & resources, plant investment
  - No outsourcing option, flexible resource assignment option
  - Implications of resource “overbooking” constraint not clear
- Extensions discussed
  - Linkage with Monte Carlo simulation
  - Capacity planning decisions
- Challenge
  - ROV formulation without explicit construction of decision tree

Summary

- MILP models can capture essential decision elements in PPD management
- Stochastic elements must be modeled using simplifications: point probability values or scenarios
- Key advantage of MILP models is comprehensive view of all decisions & interplay over time
- Joint consideration of all PPD problem features in monolithic MILP remains computationally intractable
- PPD problem provides scope for innovative decomposition strategies
- MILP decision models constitute essential components of integrated decision support strategy

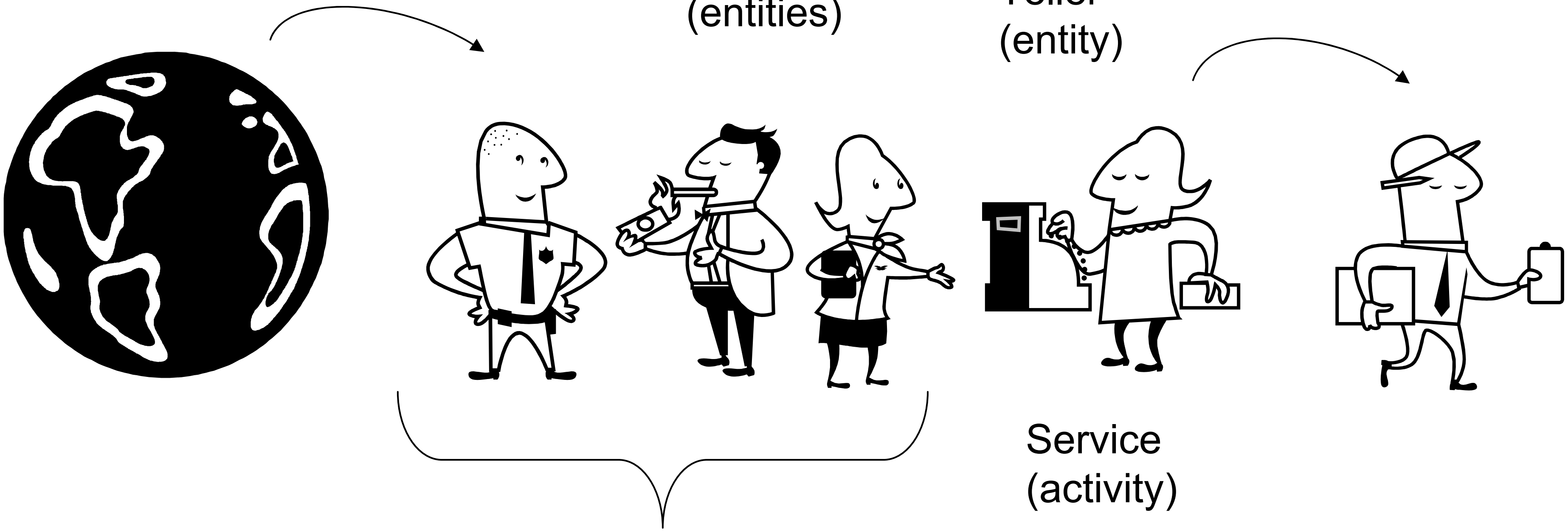
References

- Honkomp, S.J., G.V. Reklaitis, & J.F. Pekny, “Robust Planning and Scheduling of Process Development Projects under Stochastic Conditions”, 1999 AICHE Annual Mtg, Los Angles
- Jain, V. & I.E. Grossmann, “Resource-Constrained Scheduling of Tests in New Product Development”, *Ind Eng Chem Res* (1999) **38**, 3013-3026
- Maravelias, C.T. & I.E. Grossmann, “Optimal Resource Investment and Scheduling of Tests for New Product Development”, Comput *& Chem Engr* (2004) **28**: 1021-1038
- Rogers, M.J.,A. Gupta, & C.D. Maranas, “Real Options based Analysis of Optimal Pharmaceutical Research and Development Portfolios”, *Ind Eng Chem Res* (2002) **41**: 6607-6620
- Subramanian, D., J.F. Pekny & G.V. Reklaitis, ”A Simulation-Optimization Framework for Research and Development Pipeline Management”, *AICHEJ* (2001) **47**: 2226-2242

Discrete-event simulation

- Simulation
  - Imitation of the operation of a real-world process or system over time (Bank et al 1984)
- Discrete-event simulation
  - The simulation of a system by a representation in which the state variables change instantaneously at separate points in time. These points are the ones at which an event occurs (Law et al 1991)

A bank model



Interarrival
(activity)

Arrival
(event)

Clients
(entities)

Teller
(entity)

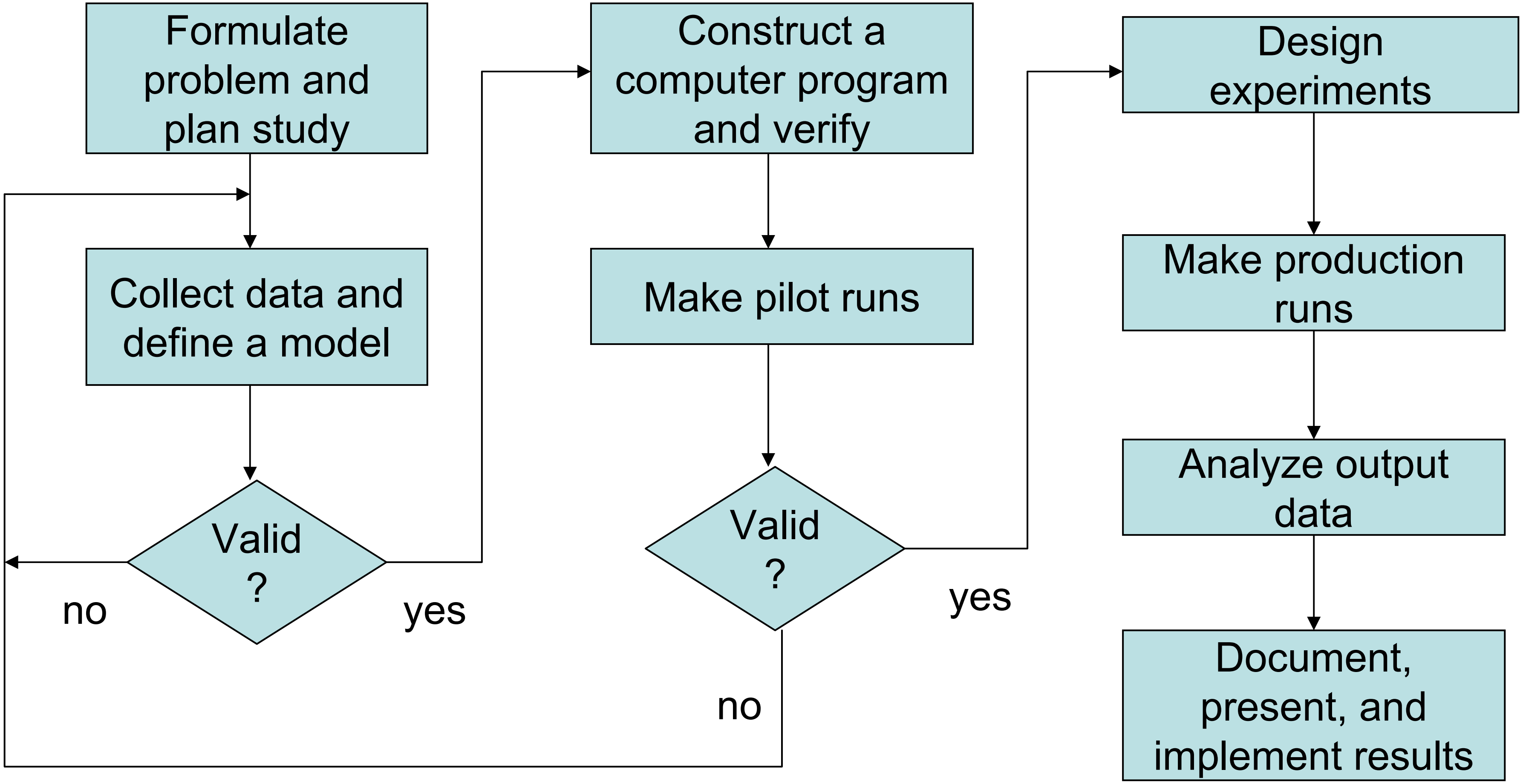
Departure
(event)

Service
(activity)

Line
(Delay)

Current state:
3 clients
Teller busy

Steps in a simulation study (Law et al 1991)



Formulate problem and plan study

Collect data and define a model

Valid ?

no

yes

Construct a computer program and verify

Make pilot runs

Valid ?

yes

no

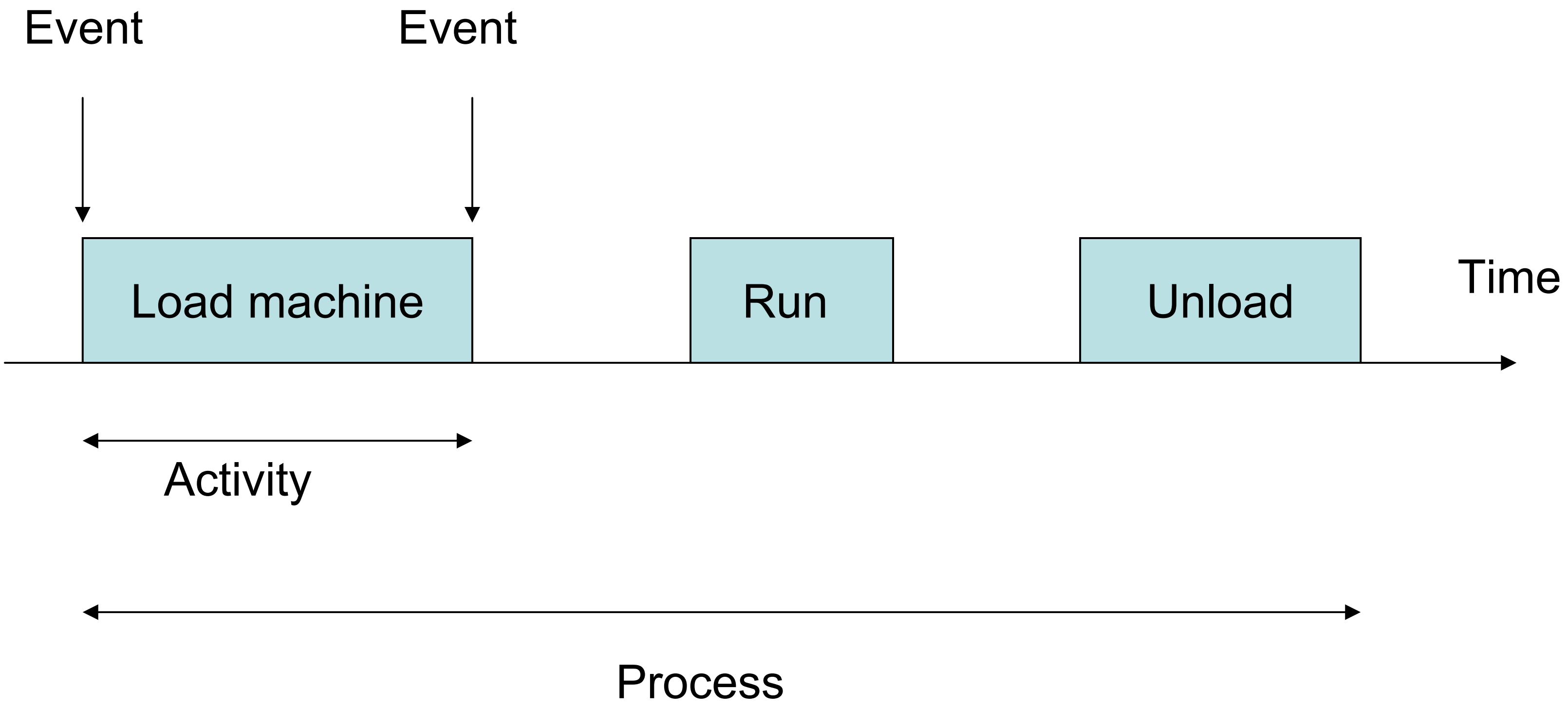
Design experiments

Make production runs

Analyze output data

Document, present, and implement results

Mechanisms to describe a discrete-event simulation



Event

Event

Load machine

Run

Unload

Time

Activity

Process

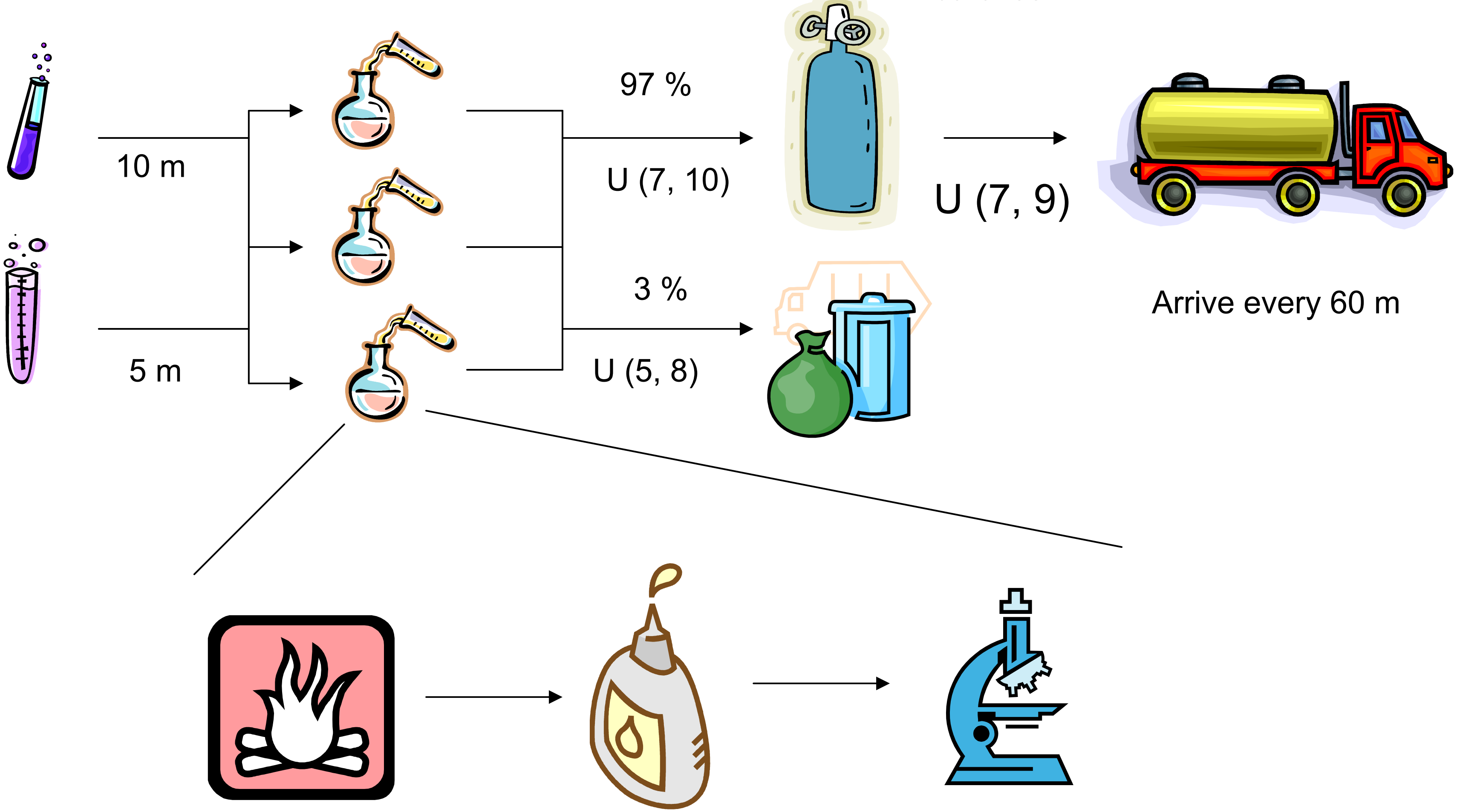
Advantages

- Study of real-world stochastic systems
- Estimate performance under different operating conditions
- Gain system insight
- Reinforce and verify analytical solutions
- Experiment with new designs and polices
- Control experimental conditions and reduce costs
- Easy to apply

Disadvantages

- Require replication to obtain statistically significant results
- Expensive and time consuming modeling
- Depend on specific operating conditions
- Overuse
- Overconfidence

Mixing plant



A

10 m

B

5 m

97 %

U (7, 10)

3 %

U (5, 8)

7 batches

U (7, 9)

Arrive every 60 m

N~(15, 0.15²) m

N~(40, 0.4²) m

Exp 10 m

Mixing plant

- The plant operates 24/7
- There are three 8 hour shifts
- There are 2 operators in charge of sampling and testing
  - 30 minute lunch break after 4 hrs into the shift
  - 15 minute break after 2 and after 6 hrs into the shift

Simulating the mixing plant with Automod*

- Loads: Dynamic entities
  - Boxes in a distribution center (DC)
  - Cars in a traffic intersection

- Resources: Static entities
  - Packers and inspectors in a DC
  - Streets, lanes and traffic lights in an intersection

- Queues: Physical space where loads can be stored
  - Real storage equipment or facilities
  - Any resource

- Order lists: Infinite capacity list of entities with some common attribute waiting to be processed
  - Allows the “communication” between the different loads
  - Parallel programming

*Automod stundent version can be downloaded from http://www.automod.com/academic/academic.html

Simulating the mixing plant

- Loads:
  - Batches
  - Trucks
  - Operators (dummy)
- Resources:
  - Mixing tanks (no necessary but recommended)
  - Operators (testing and truck filling station)
- Queues:
  - Mixing tank
  - Storage tank
  - Filling station
  - Truck parking lot
- Order list:
  - Testing
  - Storage

Testing

Outputs	Run 1	Run 2	Run 3	Run 4	Run 5	Run 6	Run 7	Run 8
average number of batches in storage	6.87	6.84	6.83	6.83	6.85	6.88	6.85	6.86
average time in storage	24606.08	24495.23	24452.59	24468.12	24547.38	24653.67	24540.14	24587.74
Total number of batches produced	1206	1206	1206	1206	1206	1206	1206	1206
utilization operator 1	0.412	0.403	0.445	0.428	0.441	0.398	0.438	0.414
utilization opertor 2	0.425	0.447	0.427	0.422	0.417	0.421	0.431	0.419

Outputs	Run 9	Run 10	Run 11	Run 12	Run 13	Run 14	Run 15	Run 16
average number of batches in storage	6.89	6.86	6.86	6.82	6.87	6.92	6.76	6.85
average time in storage	24691.05	24562.26	24578.28	24431.7	24613.34	24784.89	24225.19	24548.17
Total number of batches produced	1206	1206	1206	1206	1206	1206	1206	1206
utilization operator 1	0.404	0.409	0.417	0.433	0.426	0.428	0.424	0.399
utilization opertor 2	0.421	0.41	0.426	0.407	0.418	0.415	0.443	0.408

Outputs	Run 17	Run 18	Run 19	Run 20
average number of batches in storage	6.79	6.91	6.89	6.89
average time in storage	24319.47	24765.96	24677.29	24694.05
Total number of batches produced	1206	1206	1206	1206
utilization operator 1	0.435	0.41	0.396	0.4
utilization opertor 2	0.431	0.416	0.415	0.437

Summary

- Discrete-event simulation imitates the operation of a system that only changes in the presence of events
- A simulation study should include: problem formulation, data collection, simulation, validation and output data analysis
- There are 3 mechanisms to describe a simulation: event-driven, activity-driven and process-driven
- Main advantage: Allows to study real-world stochastic systems under different operating conditions
- Main disadvantage: Limited to a fix set of operating conditions and policies (not suitable for optimization)

Examples of graphical simulations

References

- Law Averill M, Kelton David W. Simulation modeling and analysis. New York, NY: McGraw Hill; 1991
- Banks Jerry, Carson John S. Discrete event system simulation. Englewood Cliffs, NJ: Prentice Hall; 1984
- Banks Jerry. Getting Started with Automod. 2nd edition. Chelmsford, MA: Brooks Automation; 2004

Simulation-based Approaches

- Discrete Event Simulation Basics
- Portfolio with Interdependent Products
  - Blau et al (2004)
- Simulation-based Optimization Strategy
- Portfolio Selection & Resource Scheduling
  - Subramanian et al (2003)
  - Varma et al (2005)
- Concluding Remarks

Portfolio with Interdependent Products

(Blau, G., J. Pekny, V. Varma, P. Bunch, 2004)

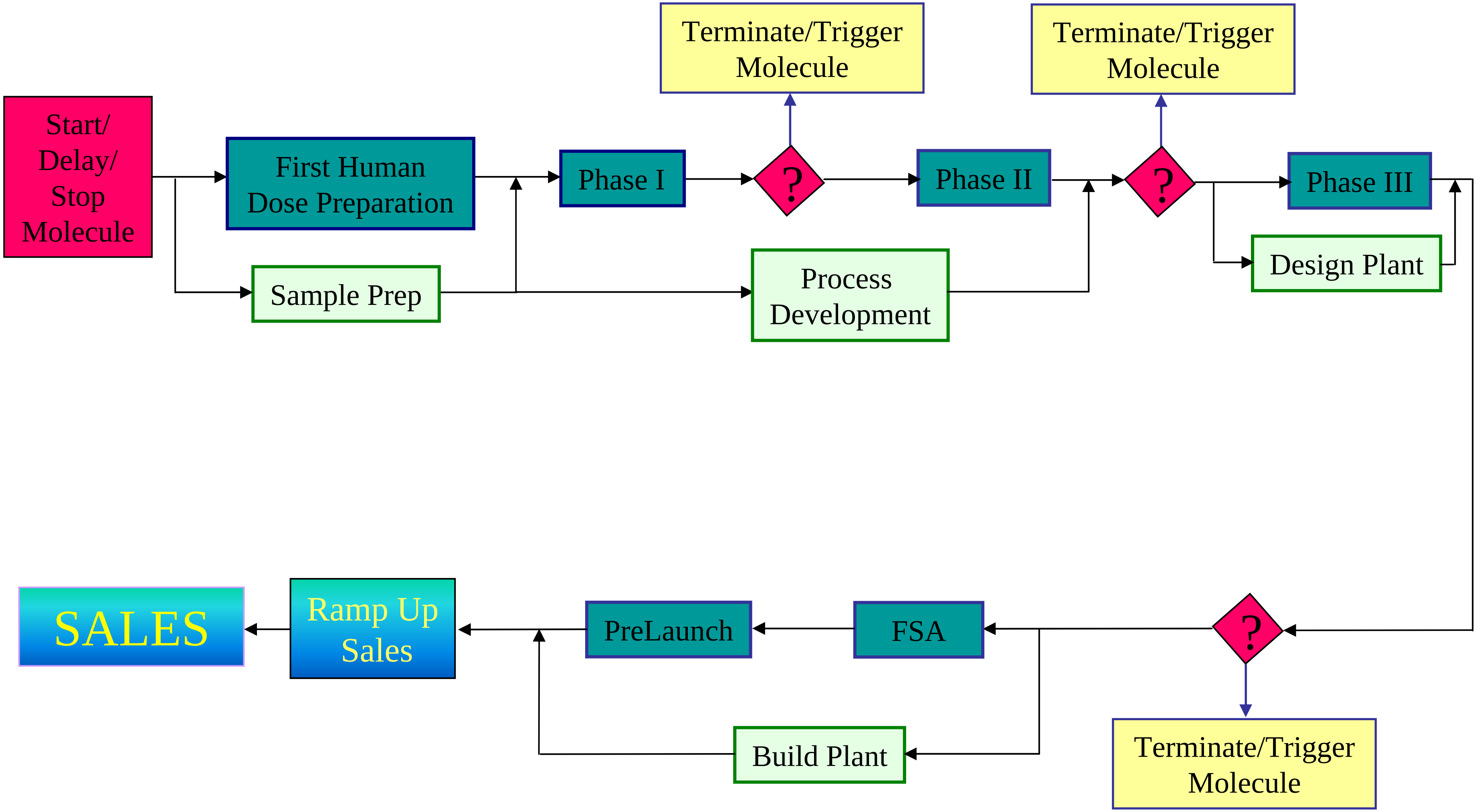
Problem Features

- Drug candidates with estimated technical success probabilities
- Uncertainties: Activity durations & costs: triangular distributions
- Uncertainties: Sales & capital costs: triangular distributions
- Financial, technical, market, manufacturing & resource interdependencies

Objective: Choose candidates based on E{NPV)
vs. risk (probability of NPV<0) trade off

- Key constraints
  - Activity specific budget resource limits
  - Capital cost budget
- Key decisions
  - Candidates selection
  - Candidate sequencing
  - Resource Assignment

Simulation model for a new pharmaceutical drug



Start/
Delay/
Stop
Molecule

First Human
Dose Preparation

Sample Prep

Phase I

?

Terminate/Trigger
Molecule

Process
Development

Phase II

?

Terminate/Trigger
Molecule

Phase III

Design Plant

?

Terminate/Trigger
Molecule

FSA

Build Plant

PreLaunch

Ramp Up
Sales

SALES

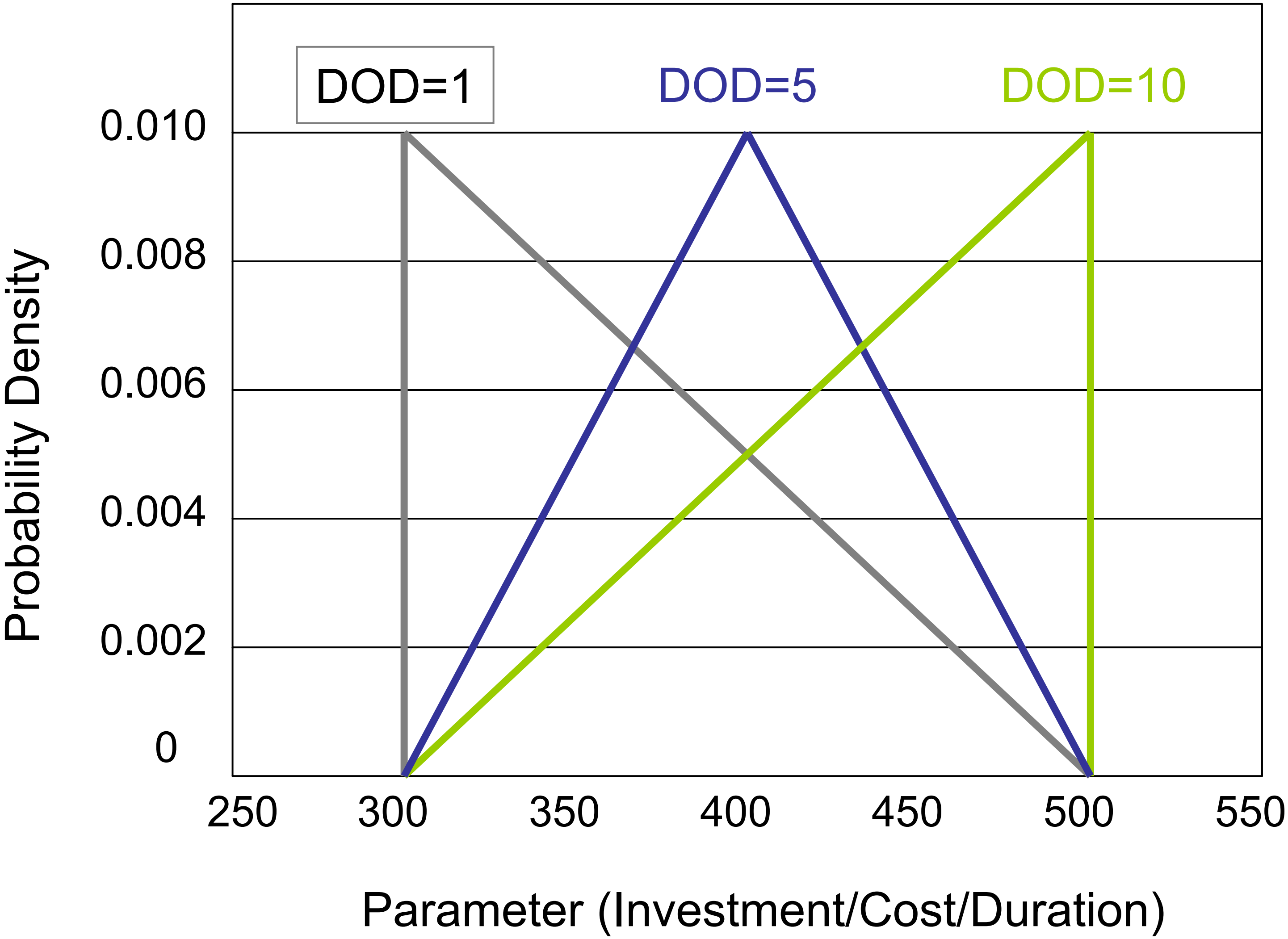
Activities Data Set

Activity	Duration(days)			Cost ($MM)			Resource($MM)
	Min	ML	Max	Min	ML	Max	
FHD Prep	100	400	500	72	80	88	273.75
Phase I	75	300	375	70	80	90	340.67
Phase II	125	500	625	75	80	85	182.50
Phase III	194	775	969	150	200	250	250.00
FSA	94	375	469	18	20	22	97.33
PreLaunch	25	100	125	45	50	55	547.50
Ramp Up 1	91	365	456	9	12	15	25.00
Ramp Up 2	91	365	456	19	22	25	50.00
Ramp Up 3	91	365	456	35	40	45	100.00
Mature Sales	91	365	456	46	53	60	150.00
Sample Prep	100	400	500	1.8	2	2.2	9.13
Process Development	200	800	1000	7	10	13	15.97
Design Plant	188	750	938	8	10	12	12.17
Build Plant	183	730	913	52	62	72	120.00

Nine Drug Data Set

Drug Name	Disease Type	**Success Probabilities**			Capital Cost			Mature Sales			Degree of Difficulty
		Phase1	Phase2	Phase3	Min	ML	Max	Min	ML	Max	
Drug1	III	0.9	0.3	0.9	40	50	60	1600	1800	2000	5
Drug2	I	0.85	0.2	0.85	20	30	40	800	1000	1500	2
Drug3	I	0.95	0.35	0.95	30	45	60	1000	1500	2000	8
Drug4	II	0.87	0.22	0.81	28	34	40	1000	2000	3000	9
Drug5	II	0.97	0.36	0.99	25	40	75	2000	2500	3000	3
Drug6	I	0.83	0.18	0.86	50	60	70	1000	1300	1600	7
Drug7	I	0.94	0.4	0.94	65	75	90	750	950	1000	1
Drug8	II	0.86	0.2	0.88	60	65	90	1000	3000	4000	4
Drug9	II	0.98	0.34	0.92	52	62	72	2000	2350	2700	10

Degree Of Difficulty: Subjective Distribution Shifting



Disease I Dependency

Type of Dependency	Explanation of the Dependency
Benefit Dependency	Sales is dependent on sequence. If two drugs of Disease I, make it successfully, then sales is 0.85 of the independent sales of each drug, if three drugs for Disease I make it, then sales is 0.75 of the independent sales, if all the 4 drugs make it successfully, the sales is equal to 0.6 times the original sales for each of the successful drugs.
Technical Dependency	If the first drug for Disease I in sequence fails, the technical success of all succeeding drugs for Disease I decrease by 50%. On the other hand, if the first drug for Disease I succeeds, the technical success of all succeeding drugs for Disease I increase by 10%.
Capital Cost Dependency	For any sequence of drugs for Disease I, the 1st drug uses full capital, the 2nd drug in sequence uses ½ of its individual capital cost, 3rd drug uses 1/3 of its capital cost, while the 4th drug uses ¼ of its capital cost.
Learning Curve Dependency	The time reduction by virtue of learning curve experience is translated into a degree of difficulty reduction of 20% for every drug in sequence for Disease I.

Disease II Dependency

Type of Dependency	Explanation of the Dependency
Benefit Dependency	Total market for the drugs of Disease II is fixed at 9000 million dollars (9 billion dollars).
Technical Dependency	If the first drug for Disease II in sequence fails, the technical success of all succeeding drugs for Disease II decrease by 50%. On the other hand, if the first drug for Disease II succeeds, the technical success of all succeeding drugs for Disease II increase by 10%.
Capital Cost Dependency	For any sequence of drugs for Disease II, the 1st drug uses full capital, the 2nd drug in sequence uses ½ of its individual capital cost, 3rd drug uses 1/3 of its capital cost, while the 4th drug uses ¼ of its capital cost.
Learning Curve Dependency	The time reduction by virtue of learning curve experience is translated into a degree of difficulty reduction of 20% for every drug in sequence for Disease II.

Input, Output and Decision Variables of Simulation model

Resource Scheduling Simulation Model

Input Data

- Probability of Success
- Associated Costs and Constraints
- Expected Sales at Maturity
- Additional sales/costs due to dependency
- Range of values for the above, uncertainty

Decision Variables

- Sequence of drug development

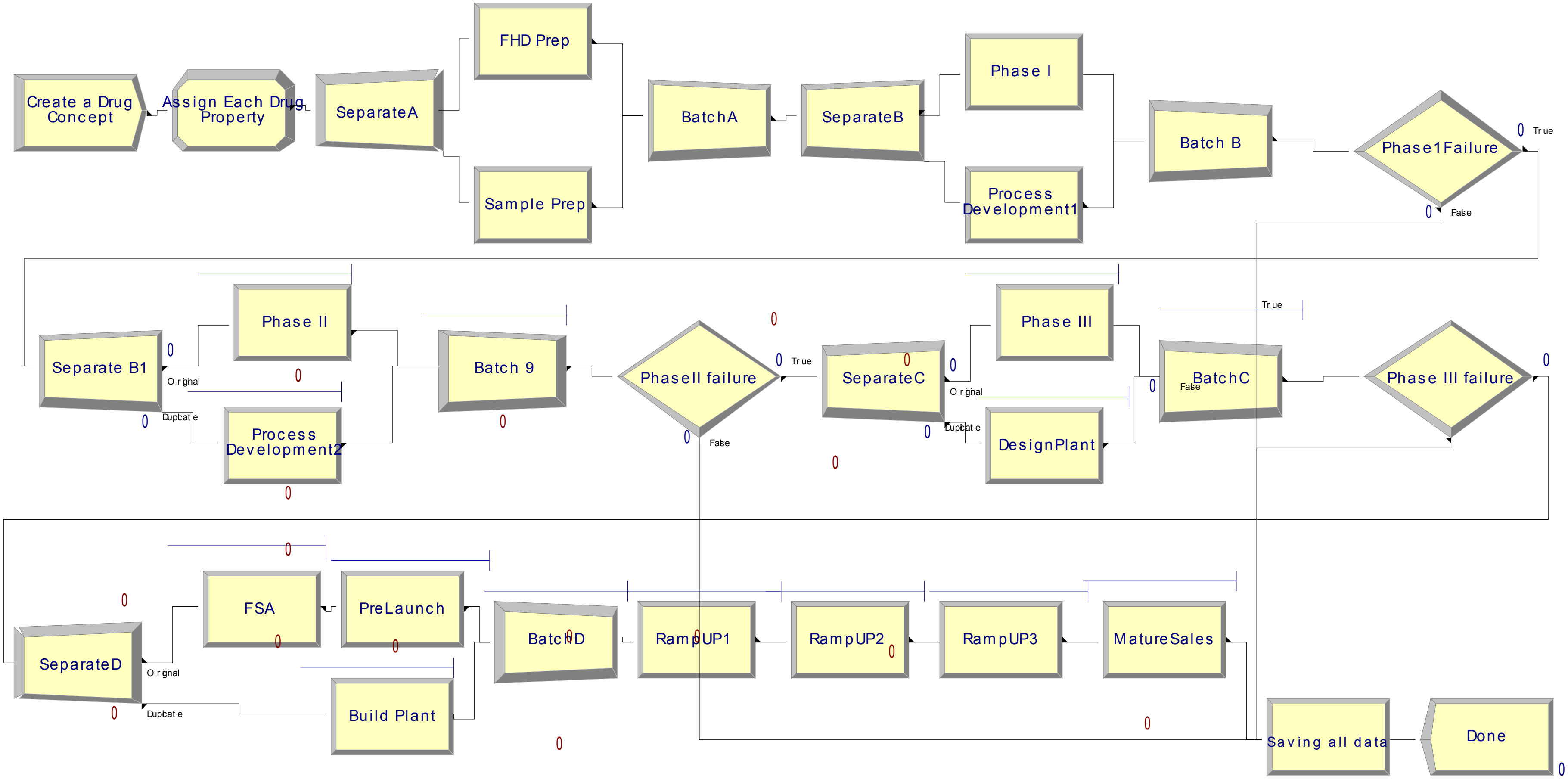
Constraint

- Resource Capacities

Output Data

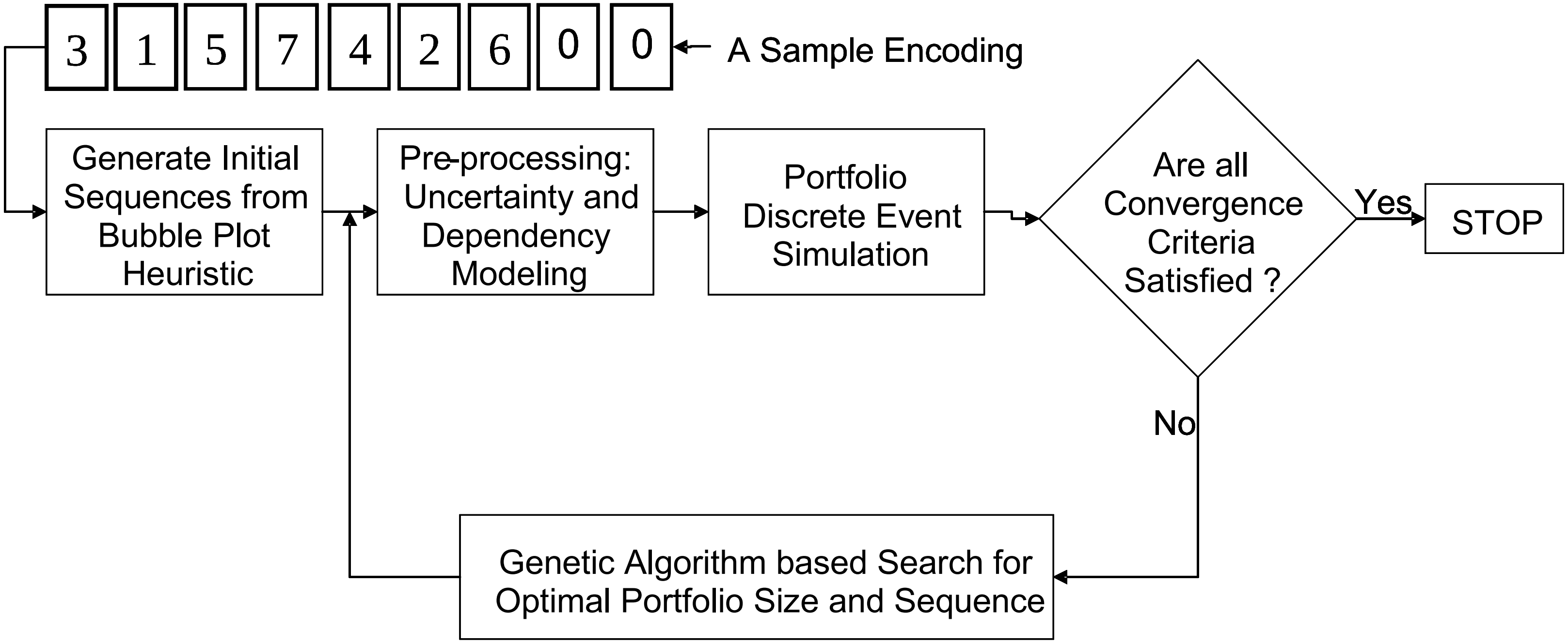
- NPV Distribution for Portfolio
- Risk Associated with Portfolio
- The schedule (sequence) of different drugs in the portfolio

Arena Simulation Model

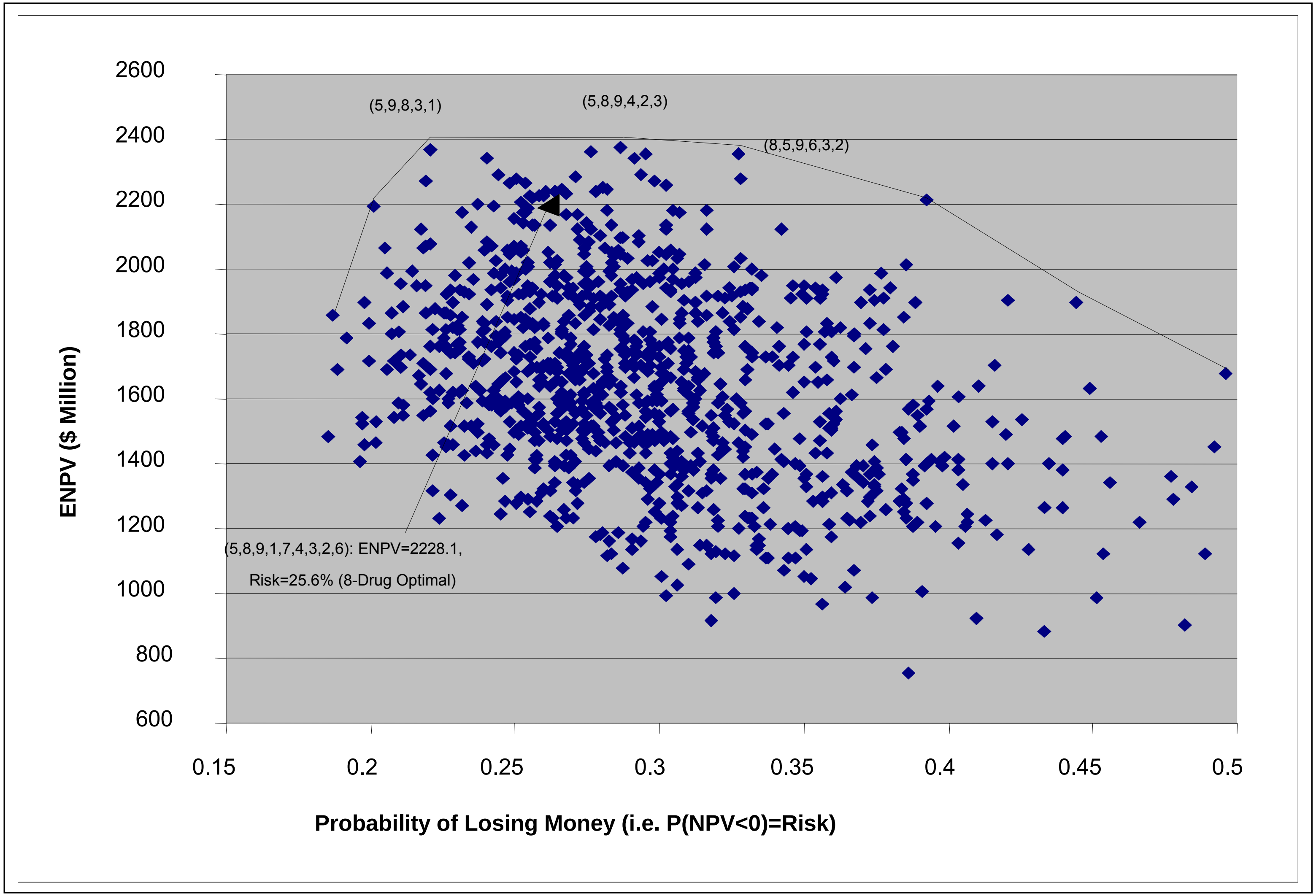


Simulation-based Search Strategy

- **Genetic Algorithm based search on sequences**
  - **Sequence provides selection & priority ordering**
  - **Use ordering for greedy assign of resources**
  - **Use 10,000 replicates to obtain good risk estimate**
- **Generate approximate Reward-Risk Efficient Frontier**



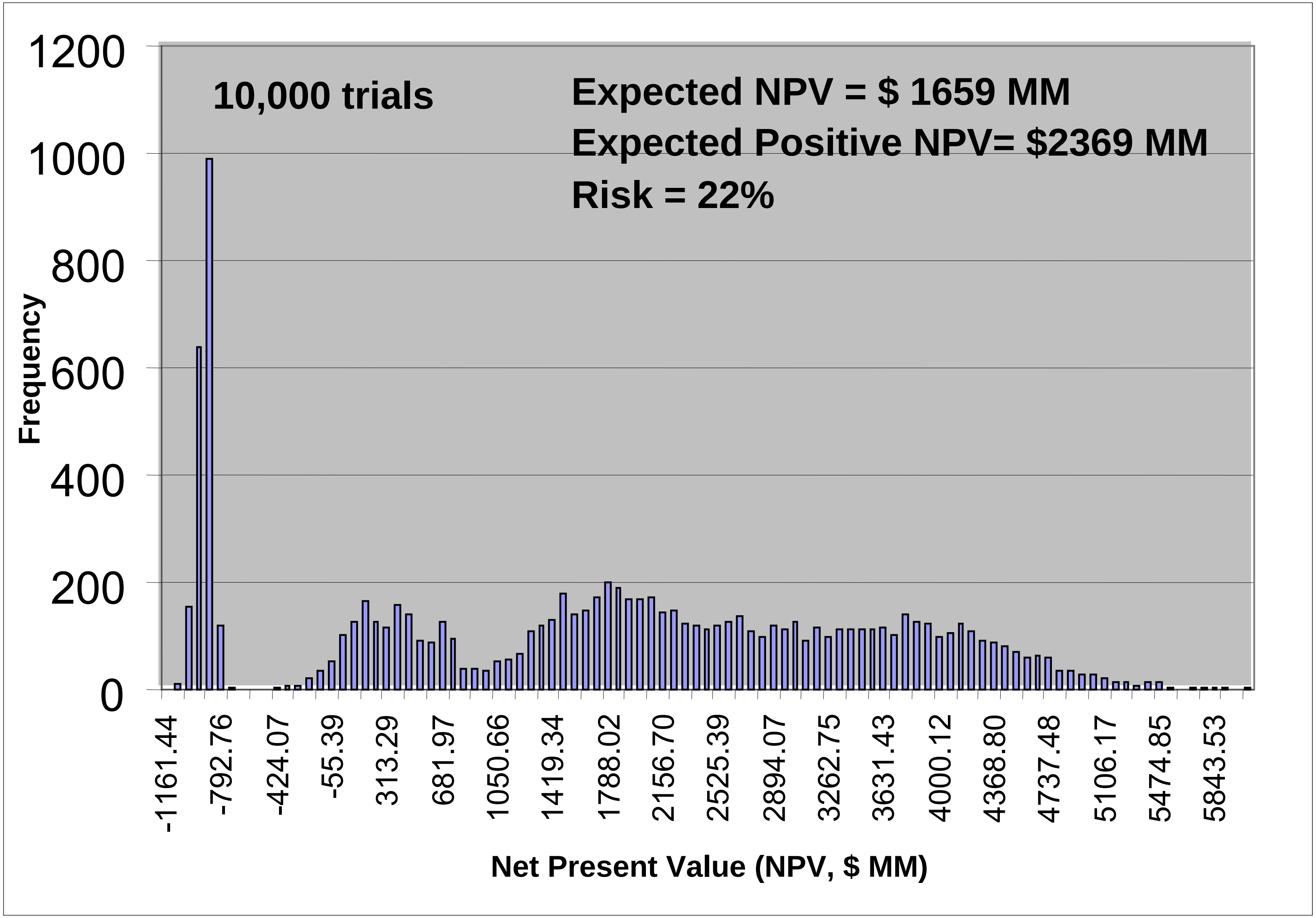
Reward-Risk Efficient Economic Frontier



Key result: 5 Drug Portfolio gives highest ENPV$ & lowest risk

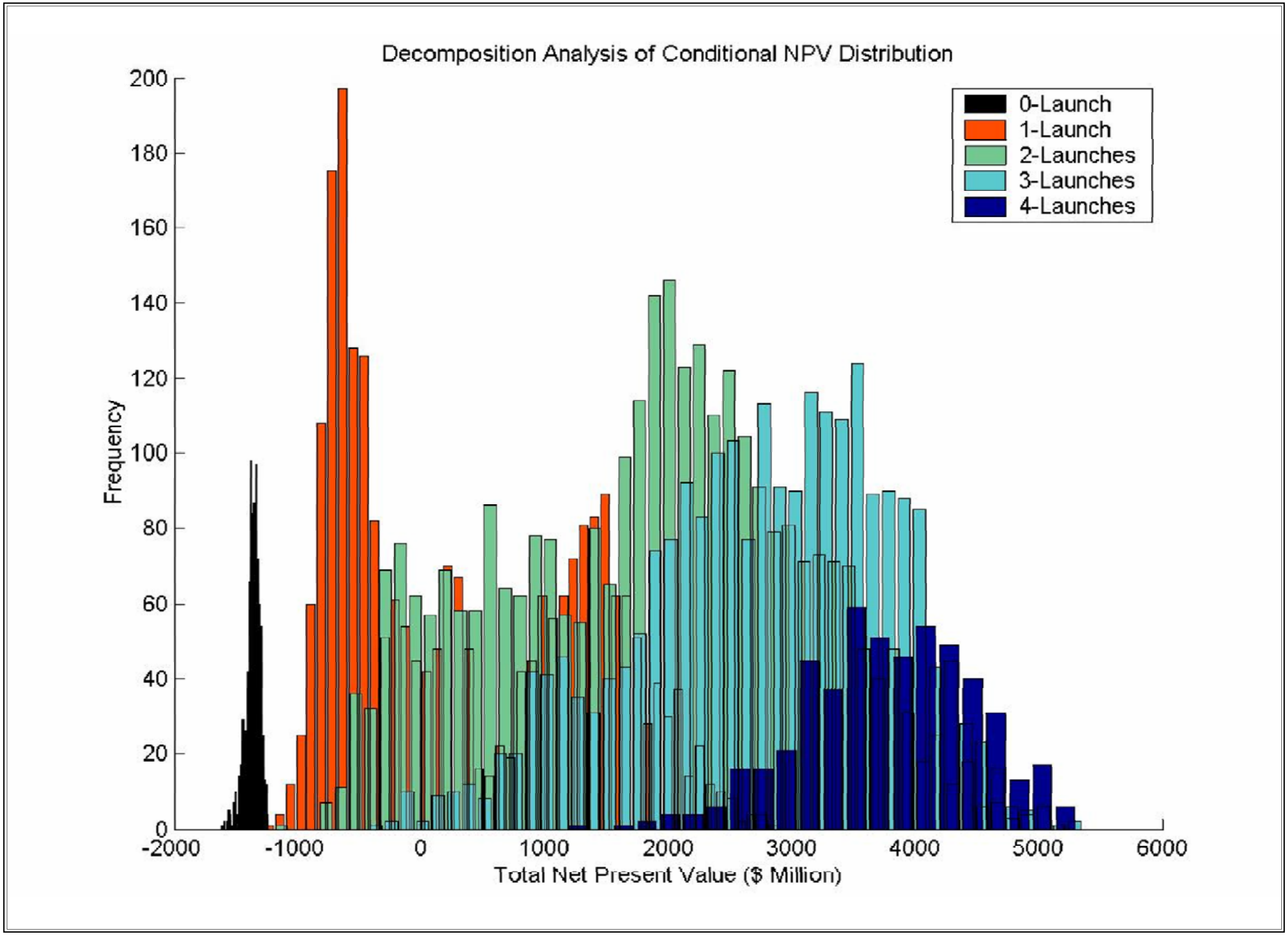
Interpretation

- Key observation:
  - Efficient frontier not monotonic
  - Efficient frontier convex function of risk
- Interdependent factors
  - Number of drugs in portfolio
  - Availability of resources
  - Impact of failures
- Interpretation
  - Large portfolio cushions impact of failures but cause resource queues & delays time to launch
  - Small portfolio reduces queuing & time to launch but effect of drug failures amplified



Net Present Value Distribution for the Best Five Drug Portfolio

Broadening of profile with number of launches



Lessons

General

- Advantages of Simulation approach
  - Accommodates uncertainties in many parameters
  - Can employ arbitrary distributions
  - Generates distribution functions & any risk measures as output
- Disadvantages
  - Requires replication to achieve statistically significant outputs
  - Uses policies/dispatching rules to make internal resource assignment decisions - suboptimal
- External parameter optimization feasible but limited to methods which can operate with unknown response surface structure

Application Specific

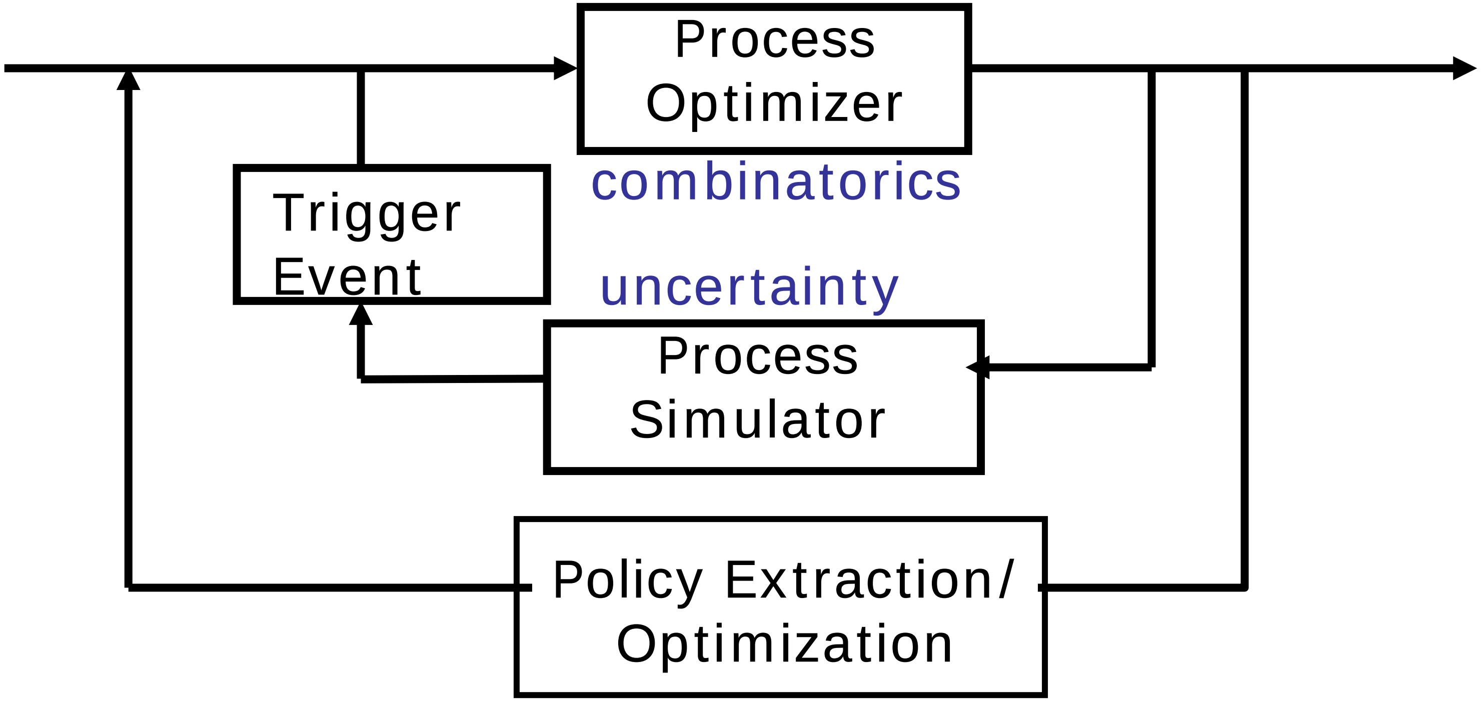
- GA search acceptable for project selection
- Dispatching rule myopic as decision tool for resource reassignment, esp. when projects fail

Sim-Opt:
Heuristic Decomposition Strategy

- ☐ Sim-Opt: Architecture to study goal oriented, resource-constrained, stochastic discrete-event dynamic systems
- ☐ Sim-Opt incorporates:
  - ☐ Monte-Carlo simulation:rigorous & realistic representation of uncertainty
    - No long range combinatorial decision making capability
  - ☐ Deterministic Optimization: long range and combinatorial decisions
    - Requires aggregate representation of uncertainty
  - ☐ Stochastic Optimization: Direct search on global system variables
    - Optimization of overall stochastic system performance
- ☐ Sim-Opt exploits mutual strengths to obtain practical but suboptimal solutions

SIM-OPT Decomposition & Architecture

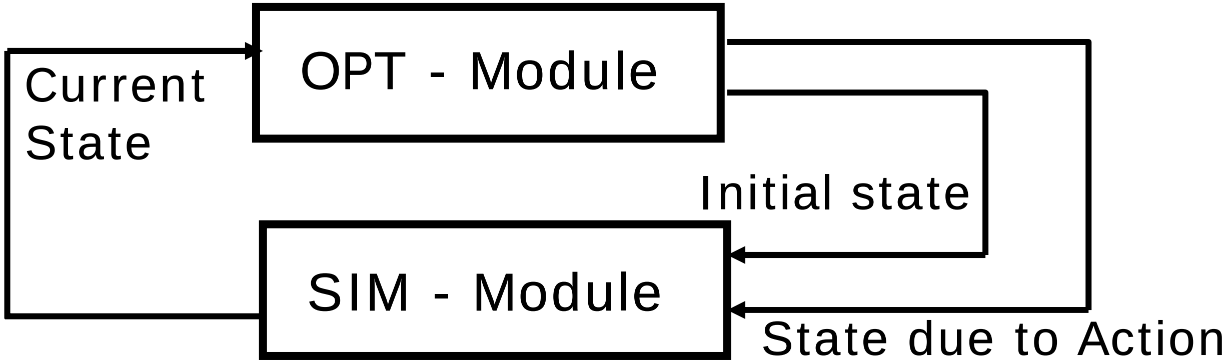
Three component decomposition



Outer loop: Use integrated information from inner loop to extract policy implications/conduct stochastic optimization

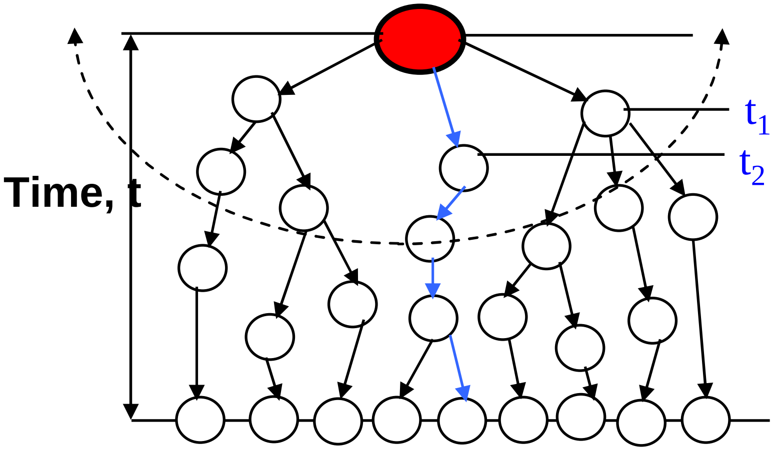
SIM-OPT Time line: A Controlled Trajectory in the Inner Loop

- SIM-OPT Inner Loop Schematic:



- Decision-Making Module (OPT) determines what "actions" to take, upon the occurrence of "events".
  - Determine priorities for task execution
- Reality Module (SIM) tracks resource-constrained evolution of "states", through stochastic state-space.

SIM-OPT Timelines



Multiple Monte-Carlo Timelines

- A timeline = controlled walk in time through the state space.
- Multiple time lines are explored in Monte-Carlo sense to gain distribution information.
- Number of required timelines determined by desired confidence limits on various distributions of interest.

SIM-OPT Outer Loop

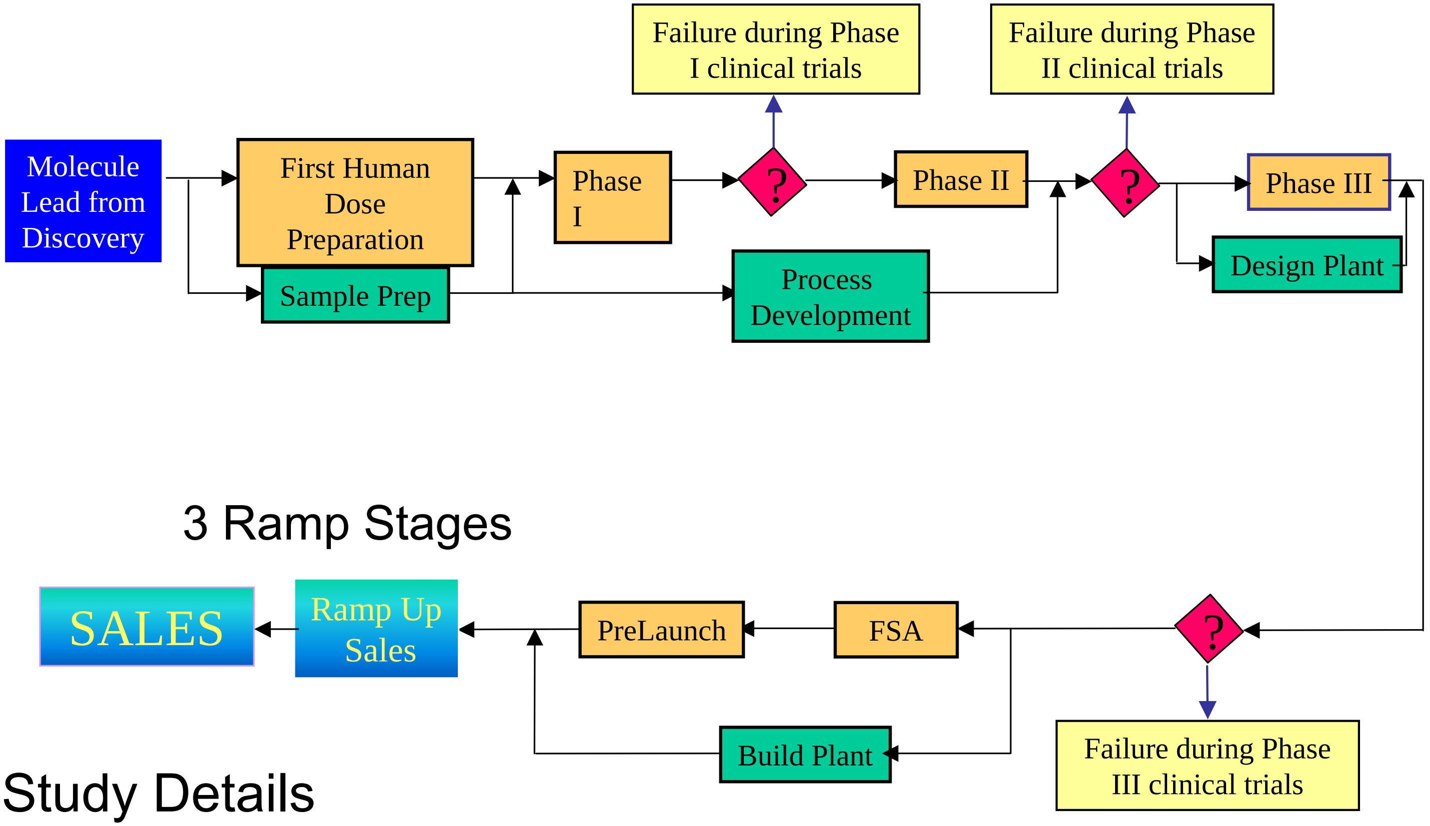
- Timelines provide complete history of how system evolved in controlled mode under uncertainty
- Analysis of timelines can
  - Identify possible undesirable future effects of Here-and-Now actions resulting from expected value optimizer
  - Identify possible desirable re-optimization / policy changes
- Aggregation of time line performance yields expected value (& higher moments) of system performance & system risk measures
- Alternative utilization of Aggregated information in Outer Loop
  - Examination of operational policies
  - Optimization of system parameters
  - Evaluation of probabilistic constraints

SIM-OPT Limitations

- SIM-OPT strategy does not generate fixed operational “solution” for whole horizon.
  - In practice “robust” fixed solution too inefficient & not used
  - Rather, plans are adjusted in response to events
- Sim-Opt can be computationally demanding.
  - Large number of invocations of optimization solver along every timeline
  - Large number of timelines to obtain valid first or higher moments of performance/risk measures
  - Inner loop constitutes expensive function evaluation for outer loop optimizer

Larger Scale Application

(Subramanian et al 2003)


Molecule Lead from Discovery

First Human Dose Preparation

Sample Prep

Phase I

Failure during Phase I clinical trials

?

Process Development

Phase II

Failure during Phase II clinical trials

?

Phase III

Design Plant

?

Failure during Phase III clinical trials

FSA

PreLaunch

Build Plant

Ramp Up Sales

SALES

3 Ramp Stages

Case Study Details
11 projects, 154 tasks,14 resources
20 yr (80 quarter) horizon

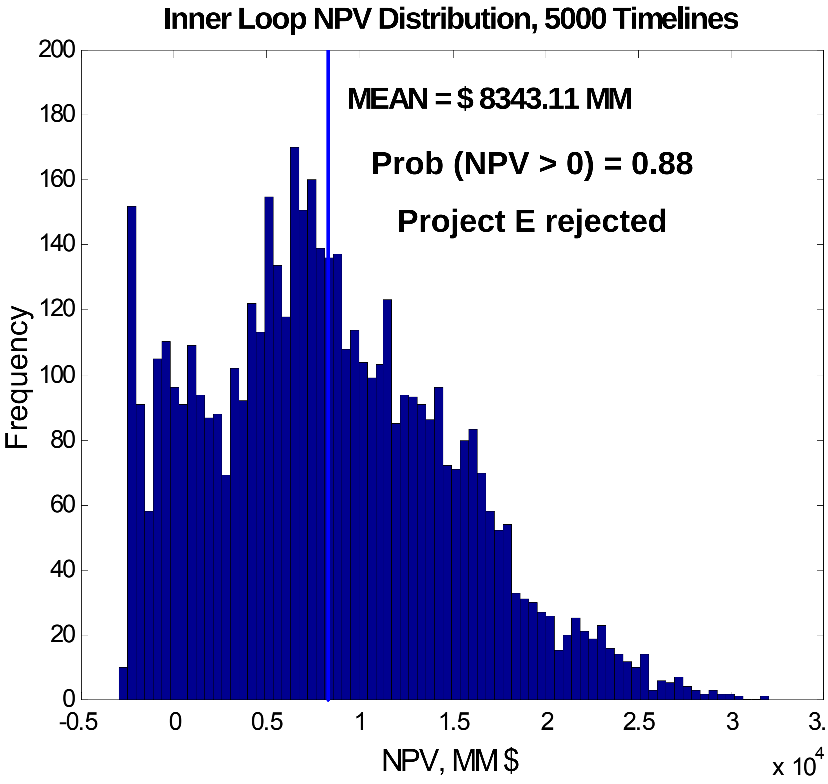
Optimization Module

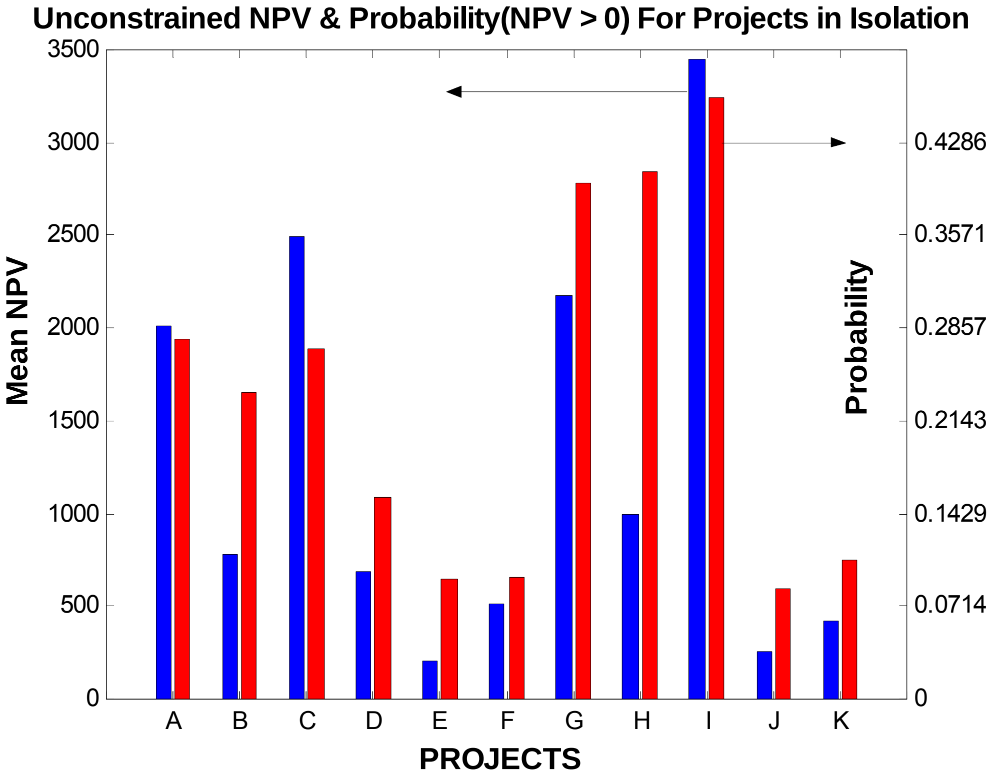
- Discrete Time MILP overbooking model
  (Honkomp et al 1999, Subramanian et al 2001)
- Objective Function:
  Expected Net Present Value
- Constraints:
  - Allocation Constraints
  - Precedence Constraints
  - Resource Constraints with Overbooking
- Rewards are function of time with penalty or reward increasing with completion time

Inner Loop Policy of Operation

- State-dependent MILP Formulation is used to react to:
  - Attrition (Failure) in the Pipeline
  - Resource Conflicts in the Pipeline
- State-dependent MILP Formulation is updated with
  - Removal of all activities of the failed project(s)
  - Removal of Finished activities of the existing projects
  - Addition of constraints to ensure seamless re-entry into SIM
  - Parameter updating for on-going activities.
- Activity Start times in the MILP Solution determine Priorities in the Simulation
  - Earlier Scheduled Starting Time ⇨ Higher Priority

5000 Inner Loop Time lines from SIM-OPT & Characterization of Projects in Isolation in SIM

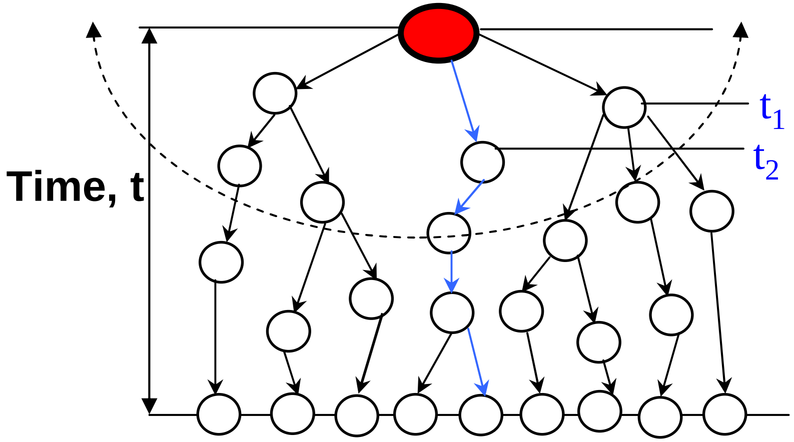




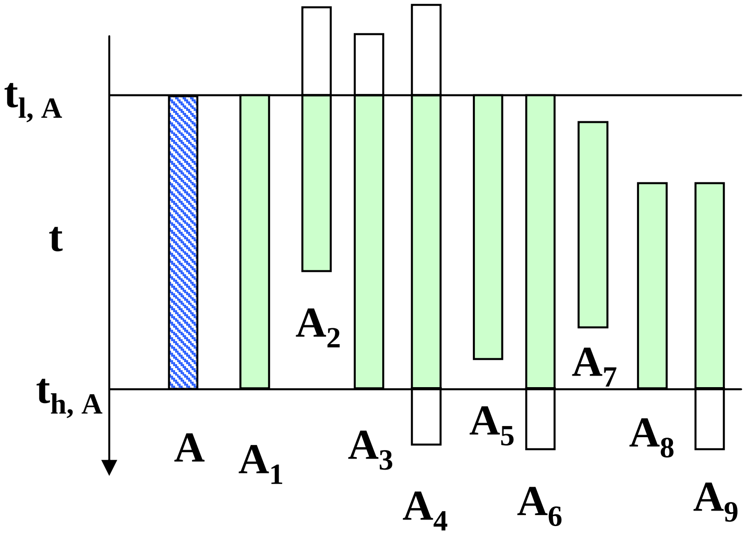
Inner Loop: Deterministic MILP decides *Policy*

Characterization of each of 11 Projects in Isolation in SIM

SIM-OPT



Multiple Monte-Carlo Timelines



Coexisting Tasks Within a Timeline

Objective of control is to:

- Decide on a Portfolio and
- Establish a *Policy* ⬄ Assign priorities to activities that compete for limited resources at various points in time, so that,
- Maximize Mean NPV & Achieve Acceptable Prob{ NPV > 0}

SIM-OPT Outer Loop

Objective of using timelines

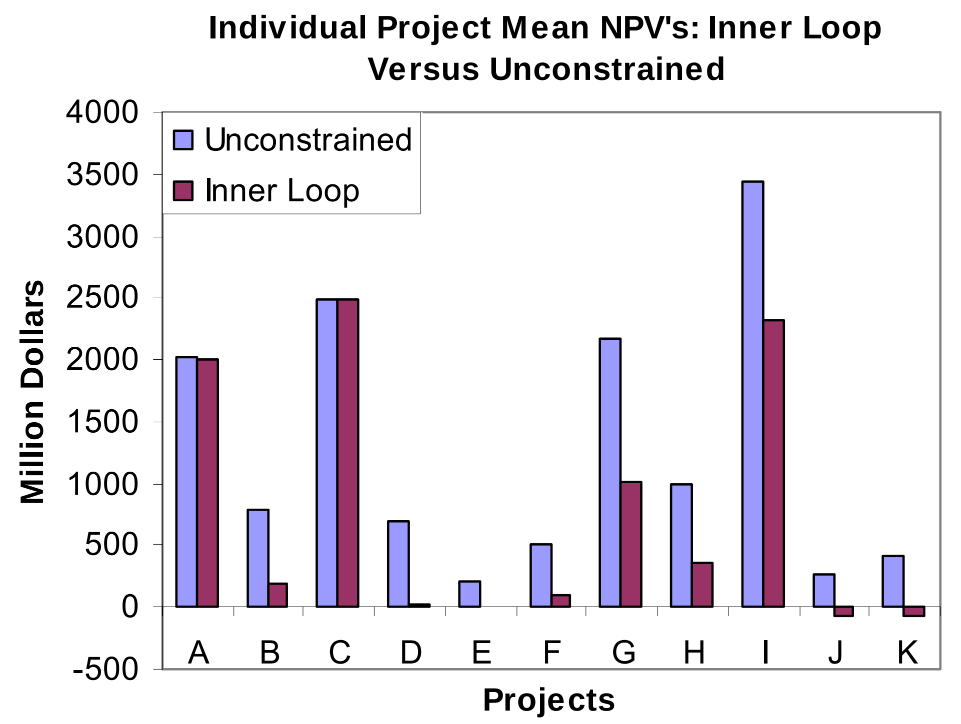
Analyze timelines to identify undesirable future effects of actions of “deterministic” optimizer

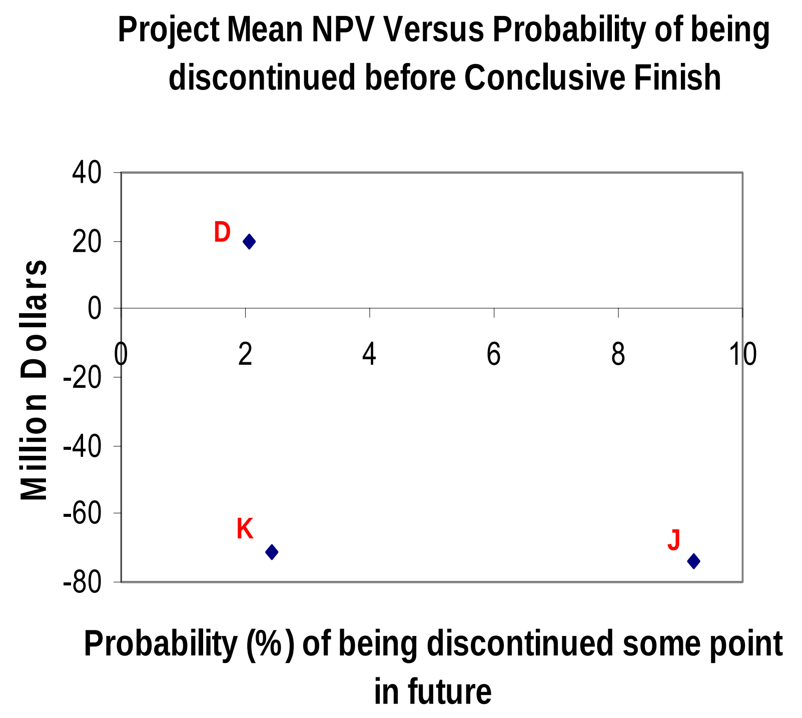
- Access available to whole history of system evolution in controlled mode under uncertainty
- Can identify undesirable future effects
- Generate insights into effective heuristics for improving solutions

Illustrative Heuristics

- Exclude projects with negative impact on portfolio mean performance (Step 1)
- Identify & exclude project that causes blocking delays in more promising project (Step 2)
- Identify & reverse priorities on project that causes delays in specific resource utilization (Step 3)

Information Integration With Respect to Portfolio Selection

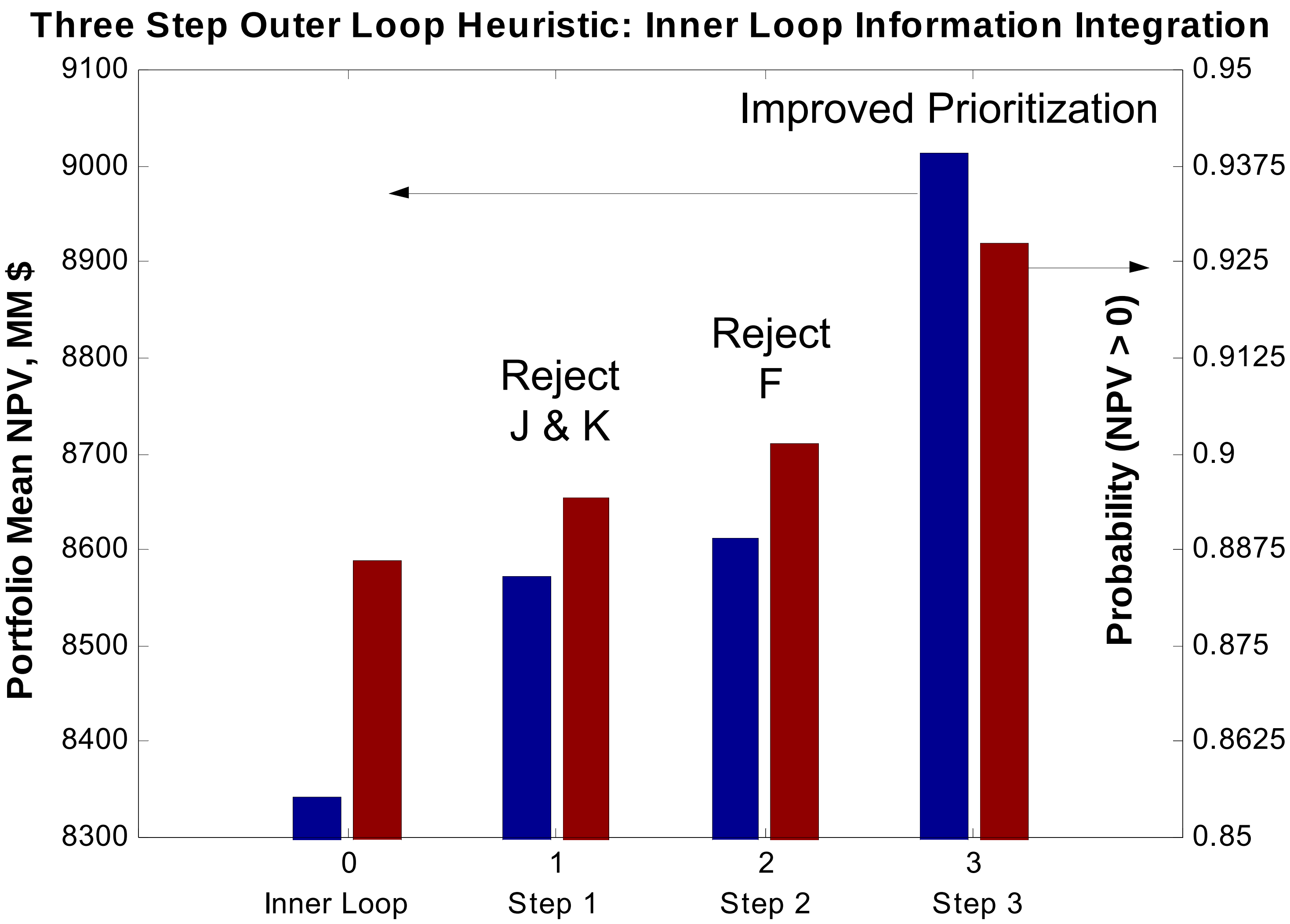

Individual Project Mean NPV's: Inner Loop Versus Unconstrained


Project Mean NPV Versus Probability of being discontinued before Conclusive Finish

Project-Centric Tracking of individual project contributions to Portfolio NPV

Project-Centric Tracking of probability of being discontinued before conclusive finish, due to becoming unprofitable wrt Patent window

Improving Stochastic Solution Using Information Integrated from Inner Loop with Three-Step Heuristic



Observations

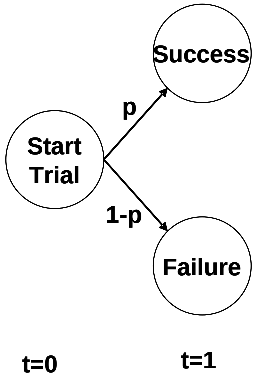
- Deterministic MILP is rough approximation of rigorous dynamic resource allocation policy for stochastic decision problem
  - Fixed project prioritization between successive MILP solutions on given timeline
  - Mean values of stochastic parameters obscure stochastic interactions
  - MILP can not address abandonment option when ENPV not promising
- Improvement obtained via stochastic dynamic scheduling & resource allocation "learned" via SIM-OPT outer-loop inference framework

Varma (2005)

Extensions: Dynamic Resource Allocation, Manufacturing & Scheduling

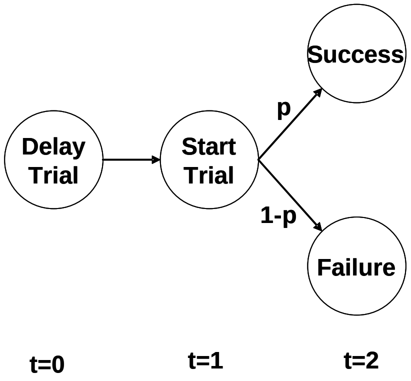
Problem Features

- Activities involve resource level vs. duration trade-offs
- Activity success & product sales are stochastic
- Pilot plant equipment shared by products
- Schedules for manufacture of clinical trial quantities must accommodate trade-offs & success probabilities



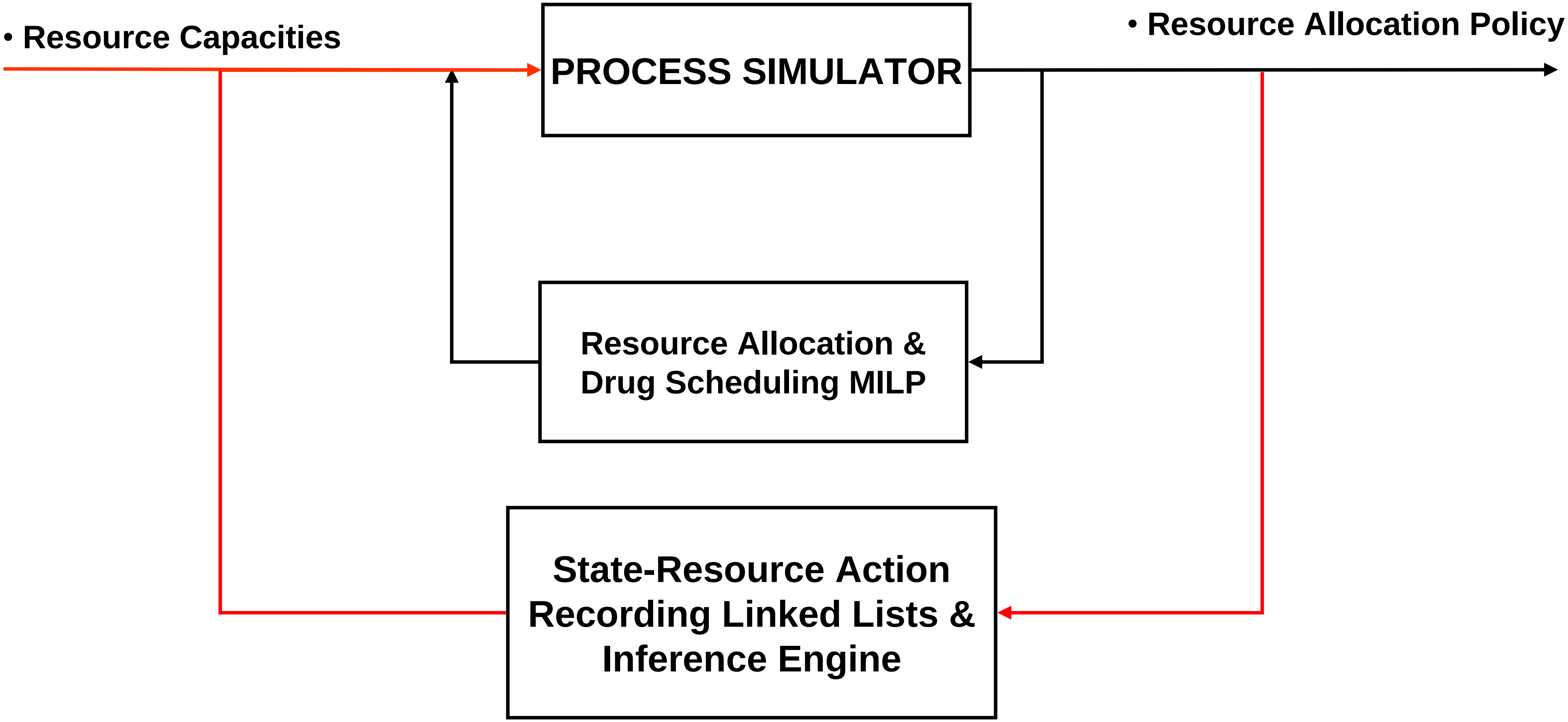
Major challenge

- Scenario-tree depends on decisions made
- Non-Markovian stochastic scheduling problem
- Rigorous approaches:
  - Neuro-dynamic programming to approximate value-to-go function (Bertsekas (2000))
  - Disjunctive formulation & Lagrangian Decomposition (Goel & Grossmann (2004))



Clinical trial started now or delayed

SIM-OPT – A Model Predictive Control Based Resource Allocation Policy Learning Framework



- Resource Capacities

PROCESS SIMULATOR

- Resource Allocation Policy

Resource Allocation & Drug Scheduling MILP

State-Resource Action Recording Linked Lists & Inference Engine

Algorithm & Software Engineering of MILP’s

- Recipe Based Variable Domain Reduction: 55% Reduction in number of binary variables
- Effective data structures for storage and access of variables for formulation generation: Over 99% improvement in formulation times over basic implementation
- Use of Allocation Constraints & Resource Constraints for “Cover Cut” generation, using ILOG Concert/ CPLEX: Solution time reduces to ~ 3 minutes vs. >6hours
- Lower bounding Heuristic using Sim-Opt for MILP in OPT:
  - An integer feasible incumbent solution within 7% bound gap.
  - 70% reduction in number of nodes (102 vs. 331) of ILOG CPLEX
  - 31% reduction in number of iterations (18818 vs. 27254) of CPLEX

Subramanian et al (2003)

Concluding Remarks

- Discrete-event simulation: important tool for studying PPD decision problems but with clear limitations
- SIM-OPT : practical framework for mitigating limitations of both math programming & simulation methods
  - Uses inner/outer loop decomposition
  - Embeds Deterministic Optimizer/Decision Module into Discrete Event Simulation
  - Uses "time line" & aggregated time line info to drive outer loop
- Flexibility in accommodating various problem features:
  - Outer loop for Optimization of global variables & probabilistic constraint satisfaction strategies
  - Policy extraction via outer loop data analysis
  - Activity cost & duration trade-offs
  - Multi-criteria via generation of Pareto optimal frontier
- Algorithm & Software Engineering key to overcoming computing burden

Demos

- Purpose:
  - Present the 2 building blocks used in the SimOpt framework
  - Illustrate the advantages and limitations of the two methodologies in dealing with stochastic systems

General features of new product development pipelines

- A number of new product candidates is available for development
- There are dependencies between the candidates
- There are resources with limited capacity
- The development of each project requires multiple activities with specific predecessor-successor relationships

General features of new product development pipelines

- Limited time horizon (first mover advantage, expiration of patents, etc)

- Variable rewards and costs

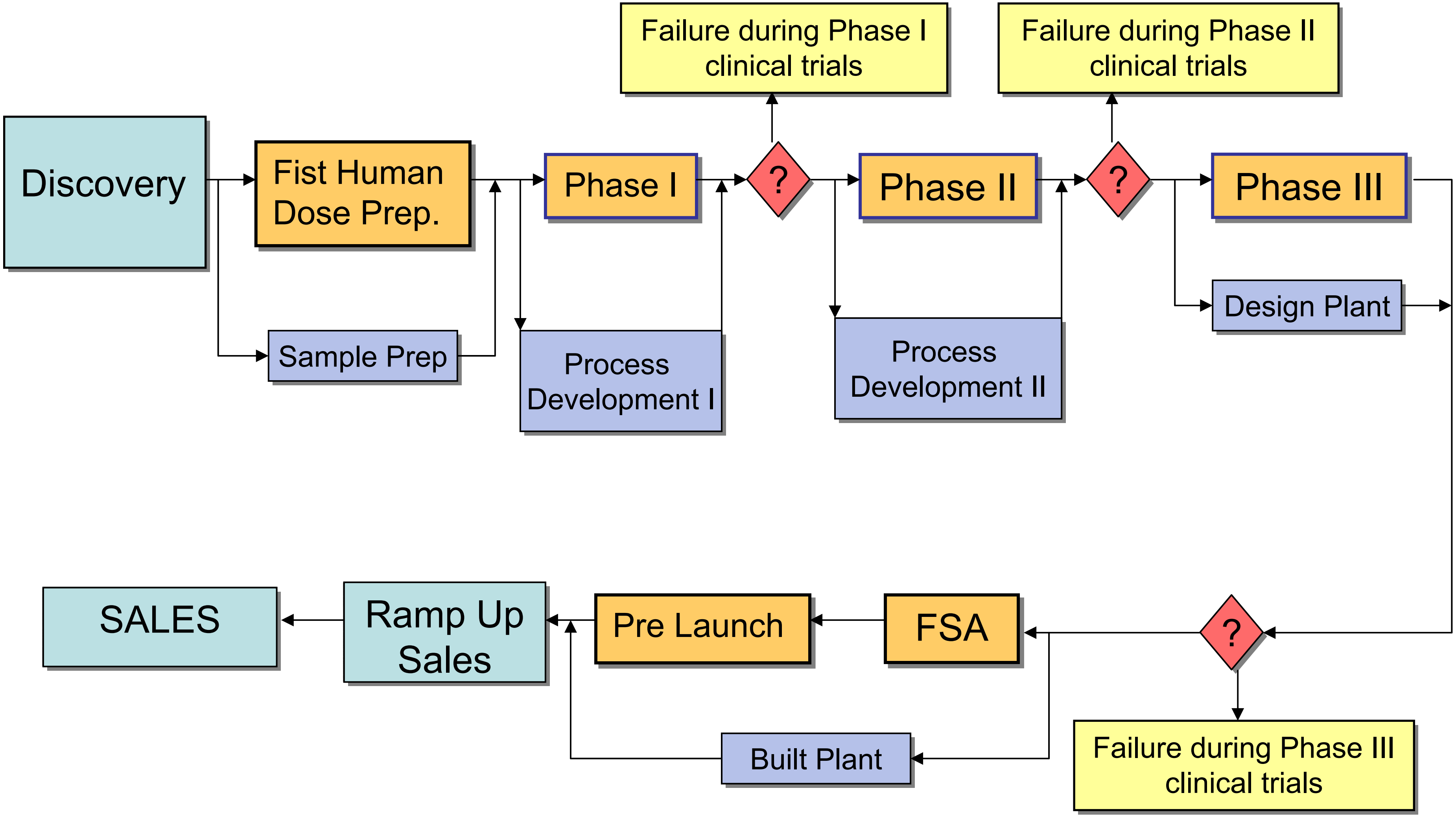
- Variable resource requirements and activities duration

- There are tasks with success/failure probability

Case study characteristics

- All the characteristics of the problem will be kept but:
  - Variable costs
  - Dependencies
  - Variable resource requirements and activities duration
- All projects will have the same resource requirements and activity durations
- The negative cash flows incurred at each stage are the same

Development



Discovery

Fist Human Dose Prep.

Sample Prep

Phase I

Process Development I

?

Failure during Phase I clinical trials

Phase II

Process Development II

?

Failure during Phase II clinical trials

Phase III

Design Plant

?

Failure during Phase III clinical trials

FSA

Built Plant

Pre Launch

Ramp Up Sales

SALES

Problem data

Activity	Mean duration (days)	Mean resource usage ($MM)	Resource capacity ($MM)
FHD Prep	400	80	275
Phase I	300	80	175
Phase II	500	80	200
Phase III	775	200	300
FSA	375	20	100
Pre-Launch	100	50	75
Ramp Up 1	365	12	25
Ramp Up 2	365	22	50
Ramp Up 3	365	40	70
Mature Sales	365	150	1000
Sample Prep	400	2	10
Process Development I	730	10	16
Process Development II	730	10	16
Design Plant	730	10	13
Build Plant	730	60	120

Problem data

Project	Phase I Succ. prob	Phase II Succ. prob	Phase III Succ. prob	Cumulative prob.	Mean Rewards*	Expected Rewards
0	90	30	90	0.243	900	218.70
1	85	20	85	0.1445	500	72.25
2	90	15	95	0.12825	2000	256.50
3	87	22	88	0.168432	1000	168.43
4	100	45	99	0.4455	200	89.10
5	90	20	86	0.1548	650	100.62
6	88	15	88	0.11616	2000	232.32
7	93	30	97	0.27063	1500	405.95
8	90	40	92	0.3312	1200	397.44

* The rewards are normally distributed (N~(u, $(0.2u)^2$)

Mathematical program nomenclature

- Indices:
  - j = a project
  - k = an activity
  - r = a resource
  - t = time
- Parameters
  - w_{jk} = The reward weight for activity k of project j (mature sales reward * cumulative probability of unresolved uncertainties)
  - a_{jk} = The duration of activity k of project j
  - k_{rjk} = The amount of resource r required by activity k of project j
  - K_r = The capacity of resource r
- Sets
  - P_{jk} = The set of activities that precedes activity k of project j
- Decision Variables
  - X_{jkt} = 1 if activity k of project j is started at time t

Mathematical program

$$\max \sum_{j=project} \sum_{k=task} \sum_{t=period} w_{jk} e^{-r\cdot(t+a_{jk})} x_{jkt}$$

Resource constraints

$$\sum_{\mathrm{j}} \sum_{\mathrm{k}} k_{rjk} \sum_{q=t-a_{jk}+1}^{t} x_{jkq} \le K_r \qquad \forall\, r,$$

Allocation constraints

$$\sum_{t} x_{jkt} \le 1 \qquad \forall\ j,k$$

Precedence constraints

$$-\sum_{t} t \cdot x_{jkt} + \sum_{t} (t + a_{jh}) x_{jht} \le T(1 - \sum_{t} x_{jkt})$$

$$\sum_{t} x_{jkt} - \sum_{t} x_{jht} \le 1 - \sum_{t} x_{jkt} \qquad \forall\ j,k,h \in P_{jk}$$

Mathematical program results

	Time horizon		
	6 years	10 years	14 years
last activity scheduled	x[0][4][13]	x[0][4][13]	x[0][6][45]
	x[1][2][5]	x[1][4][21]	x[1][4][21]
	x[2][4][9]	x[2][11][34]	x[2][13][42]
	x[3][4][14]	x[3][4][14]	x[3][4][14]
	x[4][4][18]	x[4][4][18]	x[4][4][18]
	x[5][4][17]	x[5][4][17]	x[5][4][17]
	x[6][4][10]	x[6][4][10]	x[6][12][47]
	x[7][4][5]	x[7][8][30]	x[7][11][52]
	x[8][6][13]	x[8][6][29]	x[8][7][45]
sln time (CPUs)	5	17	676
sequence	872603541	278603541	267803541

Discrete-event simulator Results

sequence	sequence criteria	ENPV ($MM)	P(NPV<0)
012345678	ENPV can be negative	-15	0.622
782345610	Prioritize 2 main projects	1760	0.4
782603541	expected rewards	1855	0.381
786203541	switch 2 projects	1843	0.379
782603514	switch 2 projects	1959	0.361
872603541	math program 6 years	1820	0.383
278603541	math program 10 years	1636	0.372
267803541	math program 14 years	1313	0.513
267830514	rewards	1308	0.508
782603	less projects in the pipeline	2521	0.355

Summary

- Mathematical programs
  - Strength: Generate optimal policies
  - Weakness: Unable to capture the complete stochastic nature of practical systems

- Discrete-event simulations
  - Strength: Captures the behavior of highly complex stochastic systems
  - Weakness: Limited scope for optimization

- Main limitation of the ENPV objective fun
  - Unable to capture the flexibilities in the system (delay or abandonment options) and control risk level

- Challenges:
  - Develop a framework that integrates information from the math program and the discrete-event simulation
  - Develop math programming approaches capable of incorporating decision making flexibilities and risk minimization

How to run the Mathematical Program

- Download the files and directories from the PASI webpage.
- Open directory Matprogram/bin (cd Matprogram/bin)
- Type OP [discretization factor] [time horizon in years] [number of projects] [resource availability factor in percentage]
- Type more solution.txt to see the results
- If you want to access the source code the header file is in the directory include and the files are in the directory src

*A secure shell can be downloaded from http://ftp.ssh.com/pub/ssh/SSHSecureShellClient-3.2.9.exe

How to use the PPD Discrete event simulator

- Download the file in the PASI webpage and open it with a browser
  - Allow blocked content if you have a pop up blocker

- Scroll down and input the sequence of projects (0-8) prioritized from top to bottom
  - Change select to 0 if you don’t want a specific project to be part of the simulation

- Click on sequence and scroll up to see the behavior of the pipeline in real time
  - Each sequence is run 5000 times

- If you want to slow down the simulation click on delay. If you want to speed it up again click on speed

- If you want to change the resource availability input the new value in the resources table and click on capacity

Take-away messages

- Product development pipeline management is important strategic decision function with enterprise-wide impact
- Product development decisions are tied very closely with strategic supply chain management, especially capacity planning
- Product development management involves solution of multistage stochastic decision problems – generally, non-Markovian
- Practical problems, especially in pharmaceutical applications, severely stress existing tools and may demand the development of new tools
- Hybrid strategies involving integration of existing tools may provide the solution for problems of practical scope