

# A Collaborative Proposal to the NSF Experimental Expeditions Program

**MCAI  
2.0**

## Computational Biology of Cancer

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# Our Vision

To gain fundamental new insights into the **emergent behaviors** of complex biological and embedded systems through the use of **revolutionary**, highly **scalable**, and fully **automated modeling and analysis techniques**.

# Primary Challenge: Scalability

## Key Scalability Issues:

**Spatial Distribution**

**Stochastic Behavior**

**Highly Nonlinear Behavior**

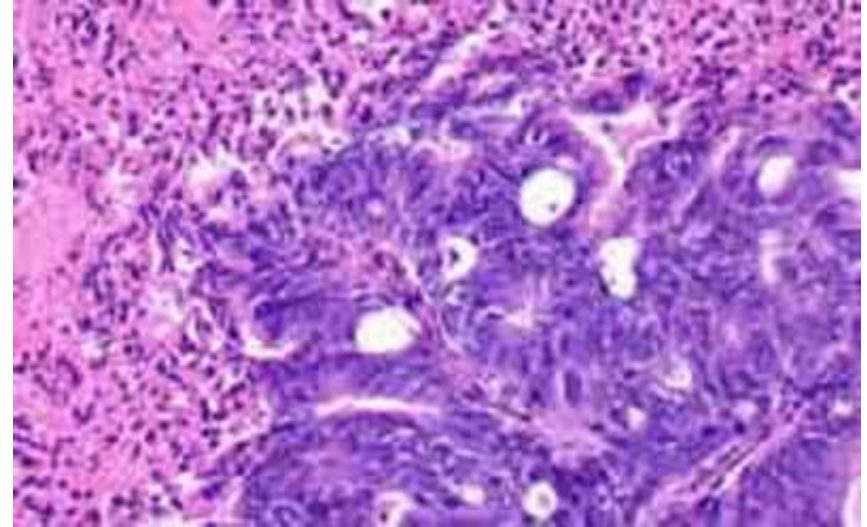
**Mixed (Hybrid) Continuous-Discrete Behavior**

**Vast Numbers of System State Variables & Components**

Complex Biological & Embedded Systems can exhibit any combination of these features

# Pancreatic Cancer

- 4<sup>th</sup> leading cause of cancer death in the US and Europe
- Five-year survival rate is only 4%
- Almost no progress in diagnosis and treatment in the past 40 years

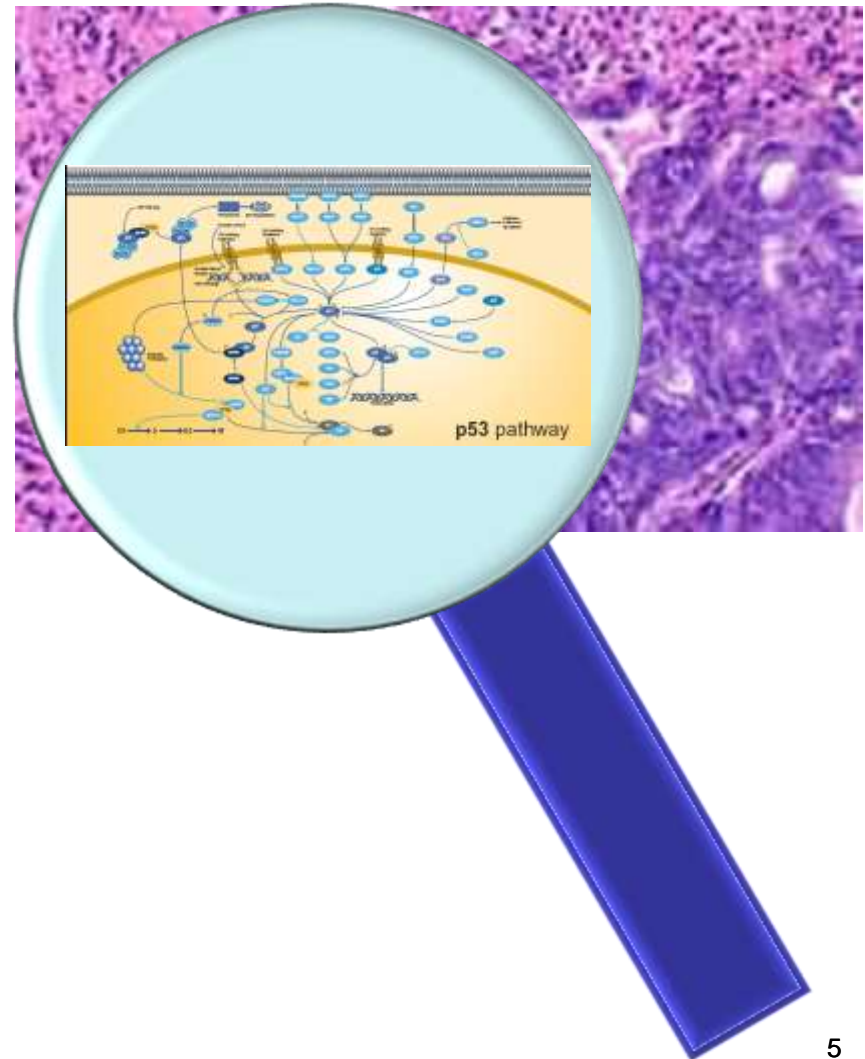


*Healthy and diseased pancreas cells*

**New insights into the dynamics of these deadly diseases are urgently needed!**

# Why Pancreatic Cancer?

- No animal model, so computational models are needed
- Signaling models from cancer experts at **TGEN** (Translational Genomics)
- We will build new analysis and verification tools
- TGEN collaborators will use tools to better understand cancer dynamics



The **Model Checking Problem**:

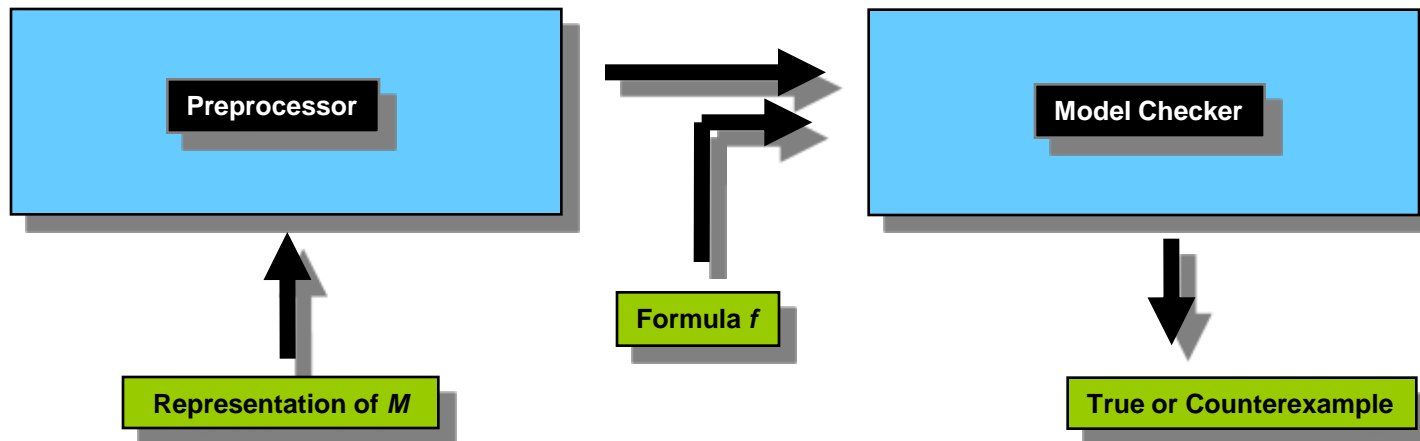
Let  $M$  be a **state-transition graph**

Let  $f$  be a **formula of temporal logic**

e.g.,  $a \text{ U } b$  means “ $a$  holds true **U**ntil  $b$  becomes true”



Does  $f$  hold along all paths that start at initial state of  $M$  ?



# Biological Models of Cancer

- Cancer as a disease of the genome...
- Cancer as a somatic evolutionary process...
- Cancer as a price of symbiosis (mitochondrial)...
- Cancer as a response to multi-cellularity...
- Cancer as a price of repair/regeneration (stem cells)...
- Cancer as a consequence of energy consumption (glucose metabolism)...
- Cancer as a response to external stress...
- Cancer as a response to the micro-environment (hyper- and hypo-methylation)...

# Relevant Biological Processes

- Proliferation:
  - Oncogenes and Tumor Suppressor Genes
- Differentiation:
  - Stem Cells...
- Signaling:
  - Kinases...
- Maintenance and Immortality:
  - Autophagy, Necrosis and Apoptosis



# War on Cancer



- “... as we know, there are **known knowns**; there are things we know we know.  
“We also know there are **known unknowns**; that is to say we know there are some things we do not know.  
“But there are also **unknown unknowns** – the ones we don't know we don't know.”
  - *Ex-US Secretary of Defense, Mr. Donald Rumsfeld, Quoted completely out of context.*

# Known Known Biology

- Theory: “World Where There Are Names for Everything.”

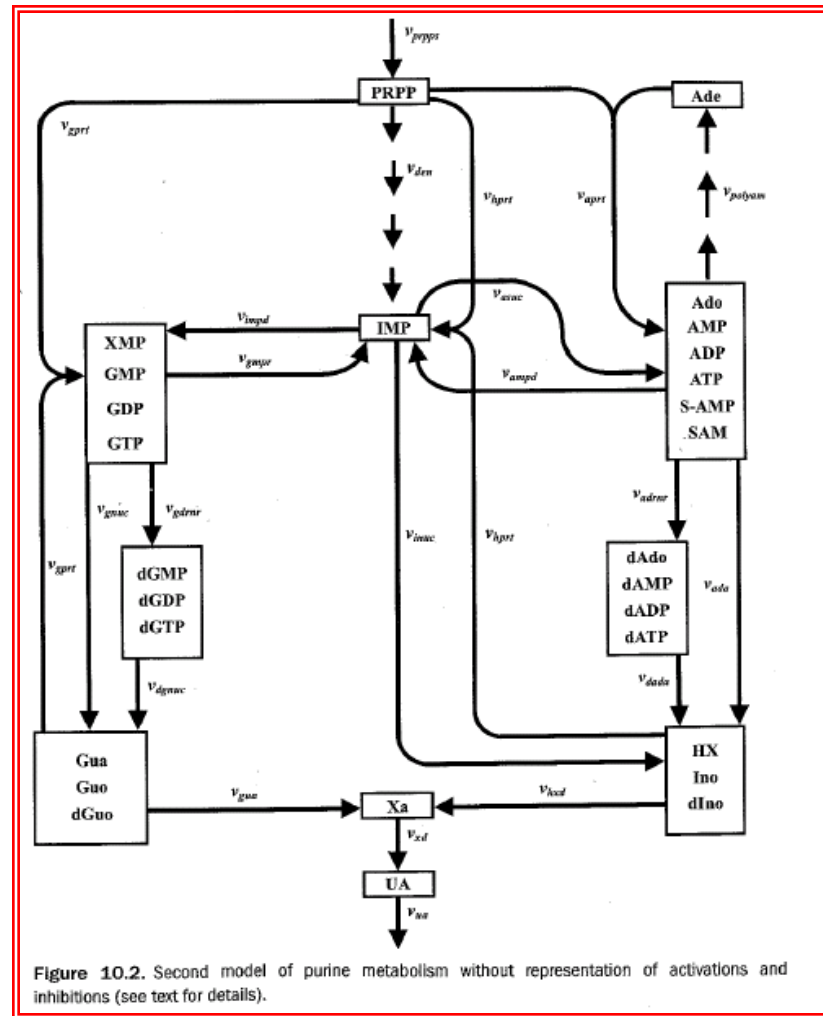
# “Addicted to Death”

- Cancer is a progressive switch from apoptotic (scheduled) to necrotic (unscheduled) tumor cell death.
- The immunobiology of many intracellular factors are involved:
  - the products of **purine metabolism** (*uric acid, ATP, and adenosine*);
  - the nuclear protein HMGB1; the S100 family members; the heat shock proteins;
- Cancer is the consequence of disordered tumor cell death rather than cell growth
  - Loss of homeostasis
  - A condition called "addicted to death."

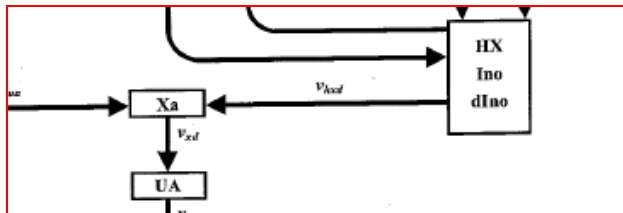
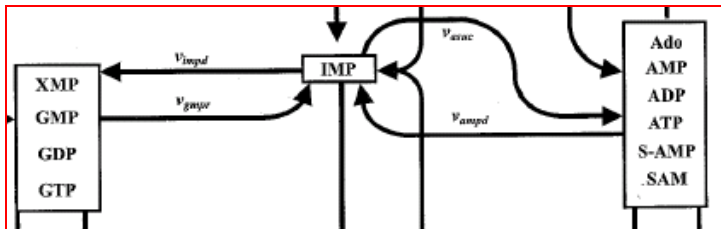
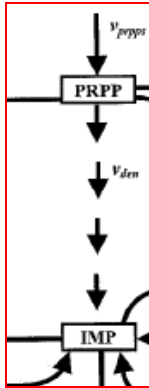
# Purine Metabolism

- **Purine Metabolism**
  - Provides the organism with building blocks for the synthesis of DNA and RNA.
- **The entire pathway is almost closed but also quite complex. It contains**
  - several feedback loops,
  - cross-activations and
  - reversible reactions

# Simple Model

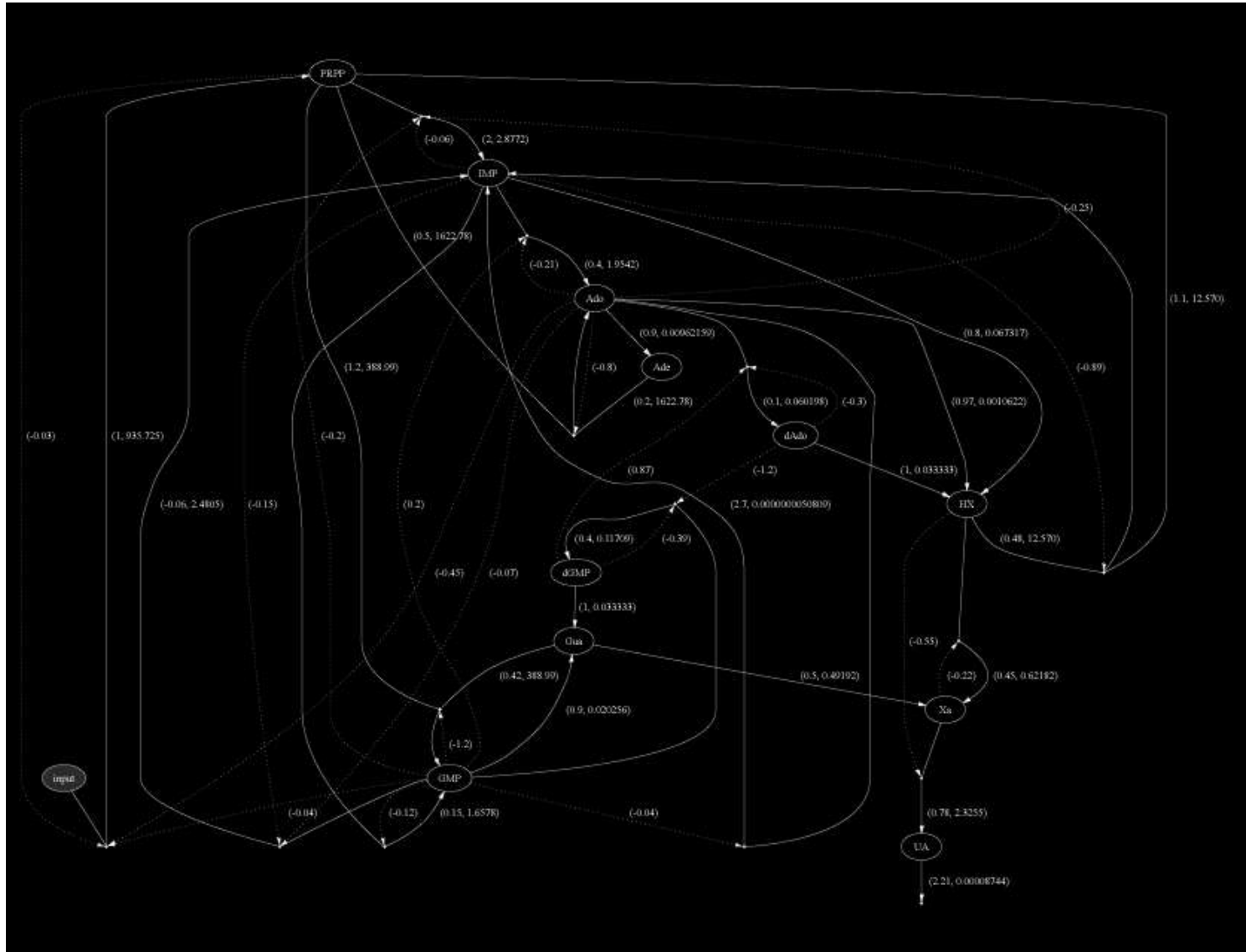


# Biochemistry of Purine Metabolism



- The main metabolite in purine biosynthesis is *5-phosphoribosyl-a-1-pyrophosphate (PRPP)*.
  - A linear cascade of reactions converts PRPP into *inosine monophosphate (IMP)*.
  - IMP is transformed into AMP and GMP.
  - Guanosine, adenosine and their derivatives are recycled (unless used elsewhere) into *hypoxanthine (HX)* and *xanthine (XA)*.
  - XA is finally oxidized into *uric acid (UA)*.

# Purine Metabolism



# Queries

- Variation of the initial concentration of PRPP does not change the steady state. **(PRPP = 10 \* PRPP1) implies steady\_state()**
- Persistent increase in the initial concentration of PRPP does cause unwanted changes in the steady state values of some metabolites.
- If the increase in the level of PRPP is in the order of 70% then the system does reach a steady state, and we expect to see increases in the levels of IMP and of the hypoxanthine pool in a “comparable” order of magnitude.  
  
**Always (PRPP = 1.7\*PRPP1) implies steady\_state()**

TRUE

TRUE



# Queries

- Consider the following statement:
  - **Eventually**  
**(Always (PRPP = 1.7 \* PRPP1))**  
**implies**  
**steady\_state()**  
**and Eventually**  
**Always(IMP < 2\* IMP1))**  
**and Eventually (Always**  
**(hx\_pool < 10\*hx\_pool1)))**
  - where IMP1 and hx\_pool1 are the values observed in the unmodified trace.
  - The model checker determines that the above statement is false..
- Counter-example: Model checker shows that the increase in IMP is about 6.5 fold while the hypoxanthine pool increase is about 60 fold.
- The model “over-predicts” the increases in products by amounts that are physiologically impossible...
- The model should therefore be amended

False

# Final Model

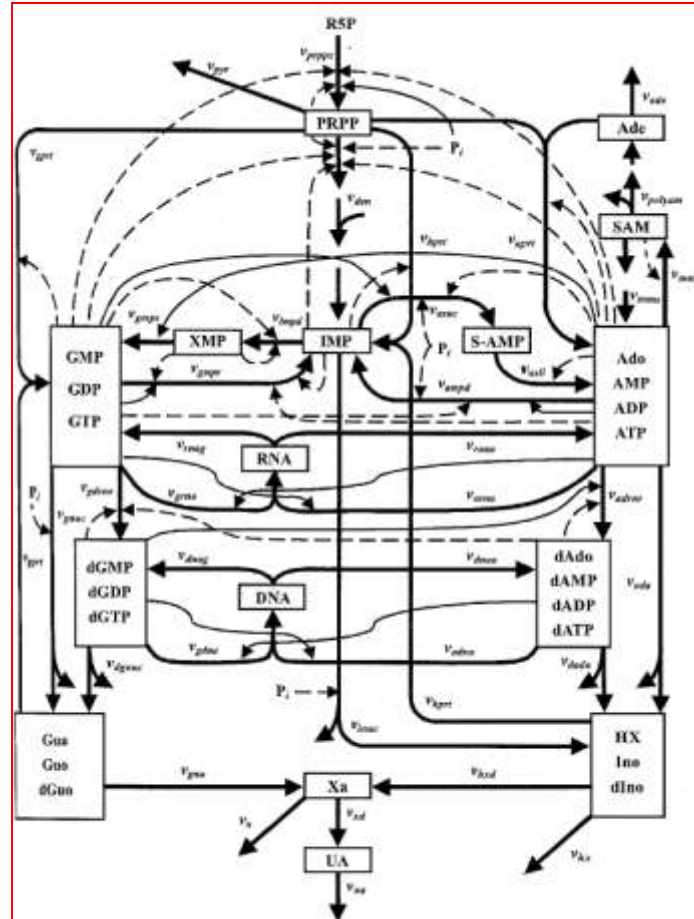


Figure 10.4. Map of the "final" model. Light solid arrows represent activation, while light dashed arrows represent inhibition. Curved heavy arrows entering or leaving the pathway indicate purine ring and ribose moieties that balance the stoichiometry of the system.



# XS-Systems:

(AAMC M. et al. 2001-2009)

## Canonical Form:

$$\left\{ \begin{array}{l} \dot{X}_i = \alpha_i \prod_{j=1}^{n+m} X_j^{g_{ij}} - \beta_i \prod_{j=1}^{n+m} X_j^{h_{ij}} \quad i = 1 \dots n \\ C_l(X_1(t), \dots, X_{n+m}(t)) = \sum (\gamma_l \prod_{j=1}^{n+m} X_j^{f_{lj}}) = 0 \end{array} \right.$$

### Characteristics:

- ◇ Predefined Modular Structure
- ◇ Automated Translation from Graphical to Mathematical Model
- ◇ Scalability

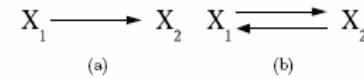


Figure 1: Representation of an unmodified and of a reversible reaction.

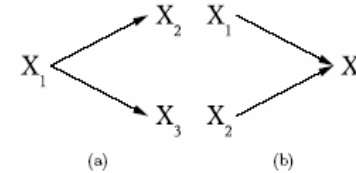


Figure 2: Representation of a divergence and of a convergence branch point (the two processes in each reaction are independent of each other).

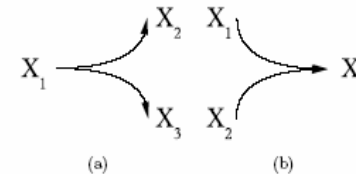


Figure 3: Representation of a single splitting reaction generating two products,  $X_2$  and  $X_3$ , in stoichiometric proportions and of a single synthetic reaction involving two source components,  $X_1$  and  $X_2$  always in stoichiometric proportions.

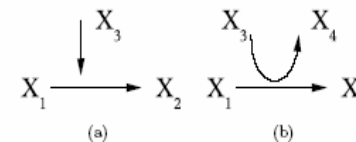
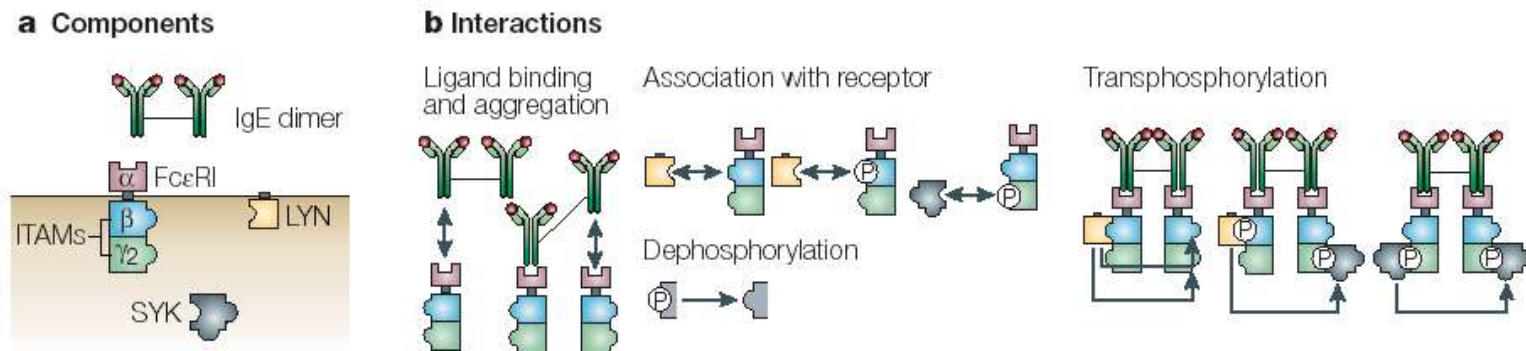


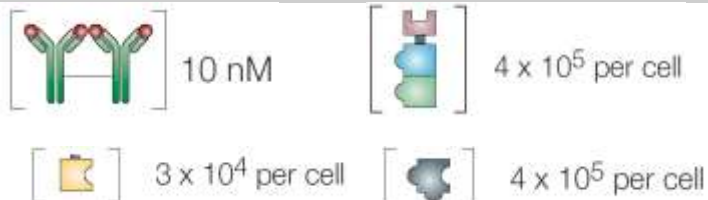
Figure 4: The conversion of  $X_1$  into  $X_2$  is modulated (stimulation or inhibition is represented by the sign of the arrow) by  $X_3$ . The reaction between  $X_1$  and  $X_2$  requires coenzyme  $X_3$ , which in the process is converted into  $X_4$ .

# Rule-based modeling protocol

1. Define components as *structured objects* and interactions as *rules*.

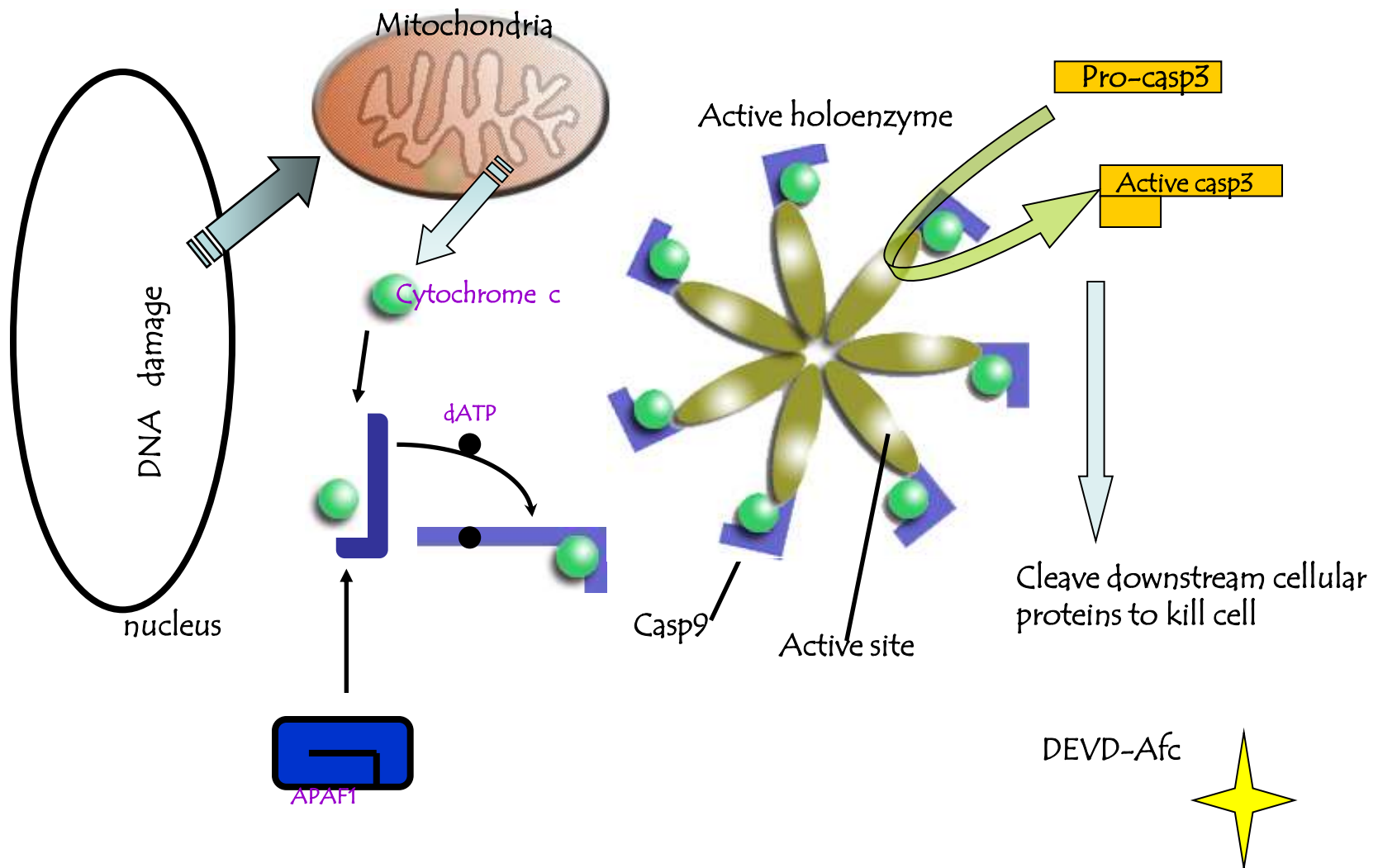


2. Determine **concentrations** and **rate constants**

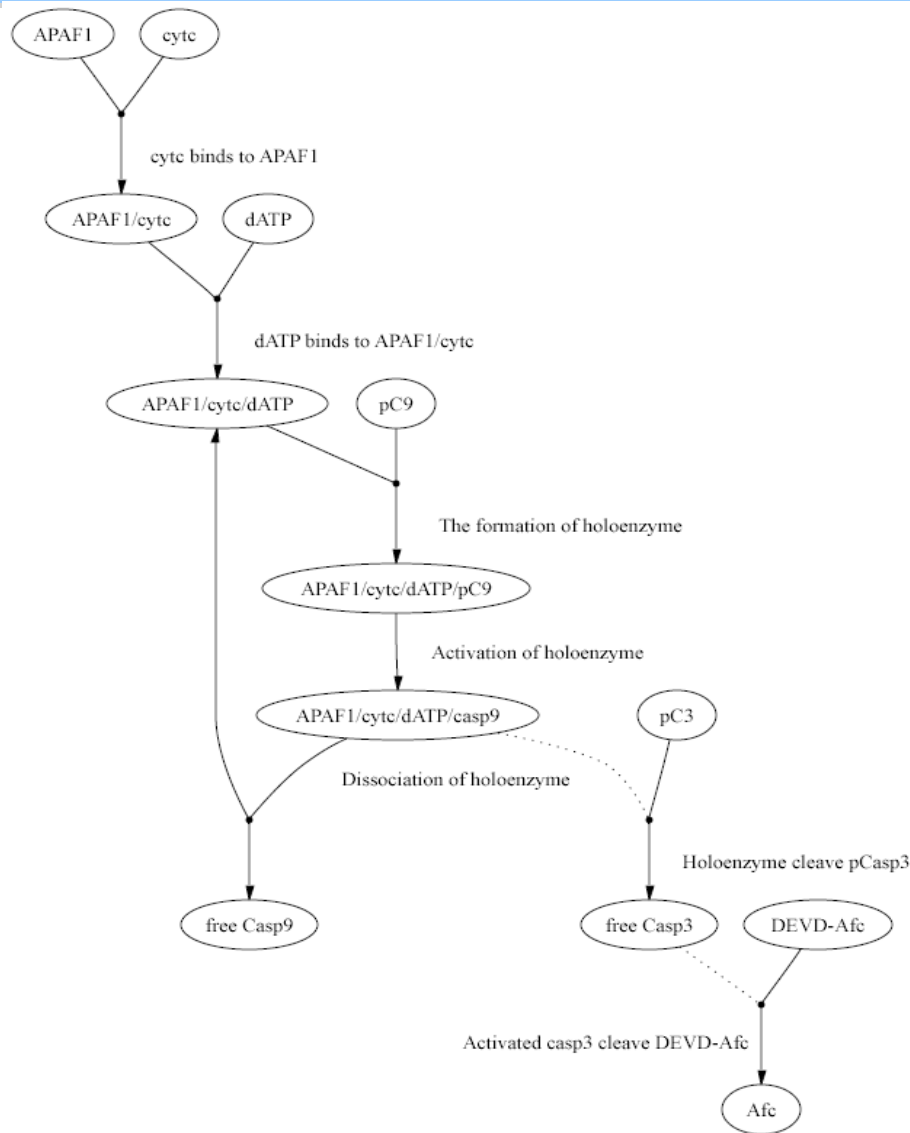


3. Generate and simulate the model.

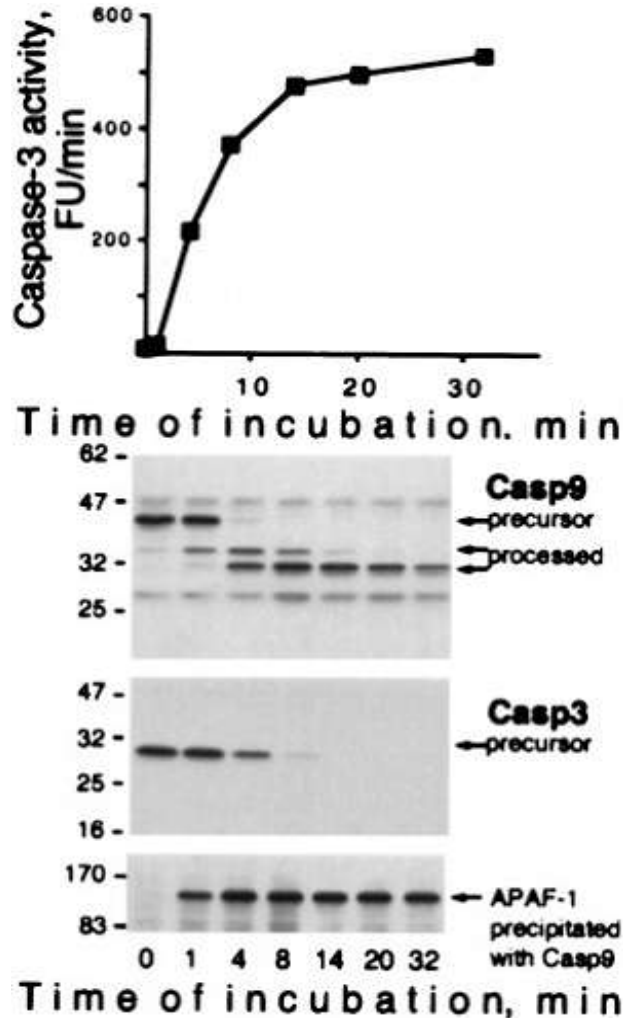
# The activation of Casp9 needs APAF1 and cytochrome c



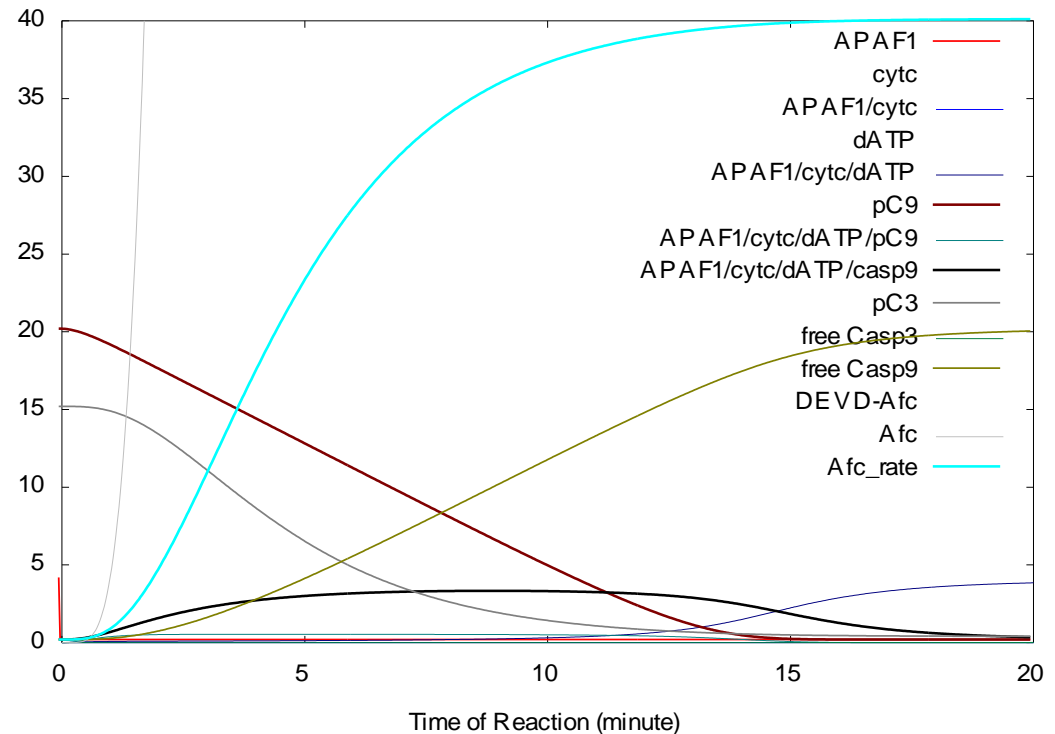
# xS-System Model



# Simpathica recapitulate the holoenzyme formation process



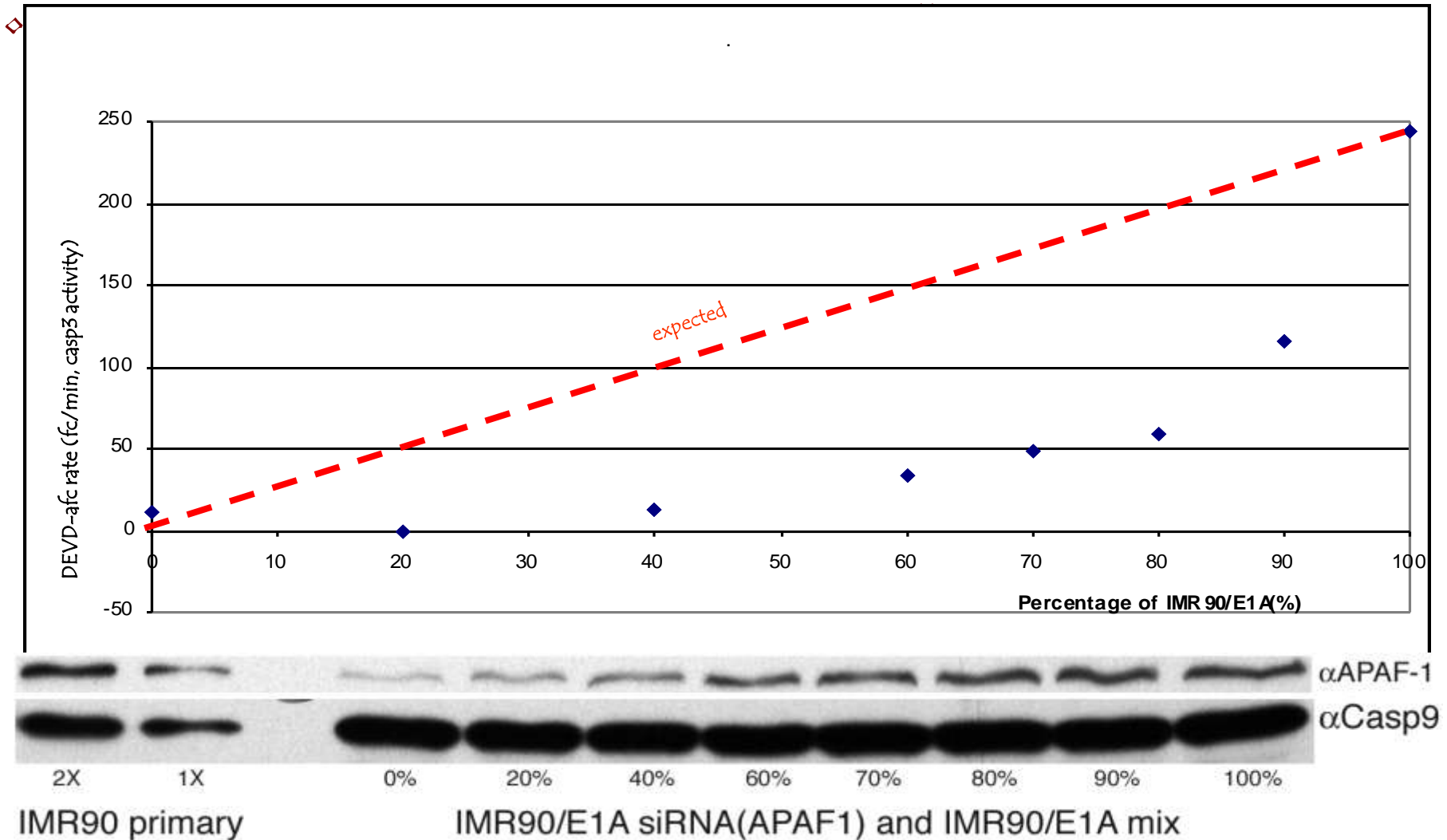
The Simulation of Apoptotic Holoenzyme Kinetics



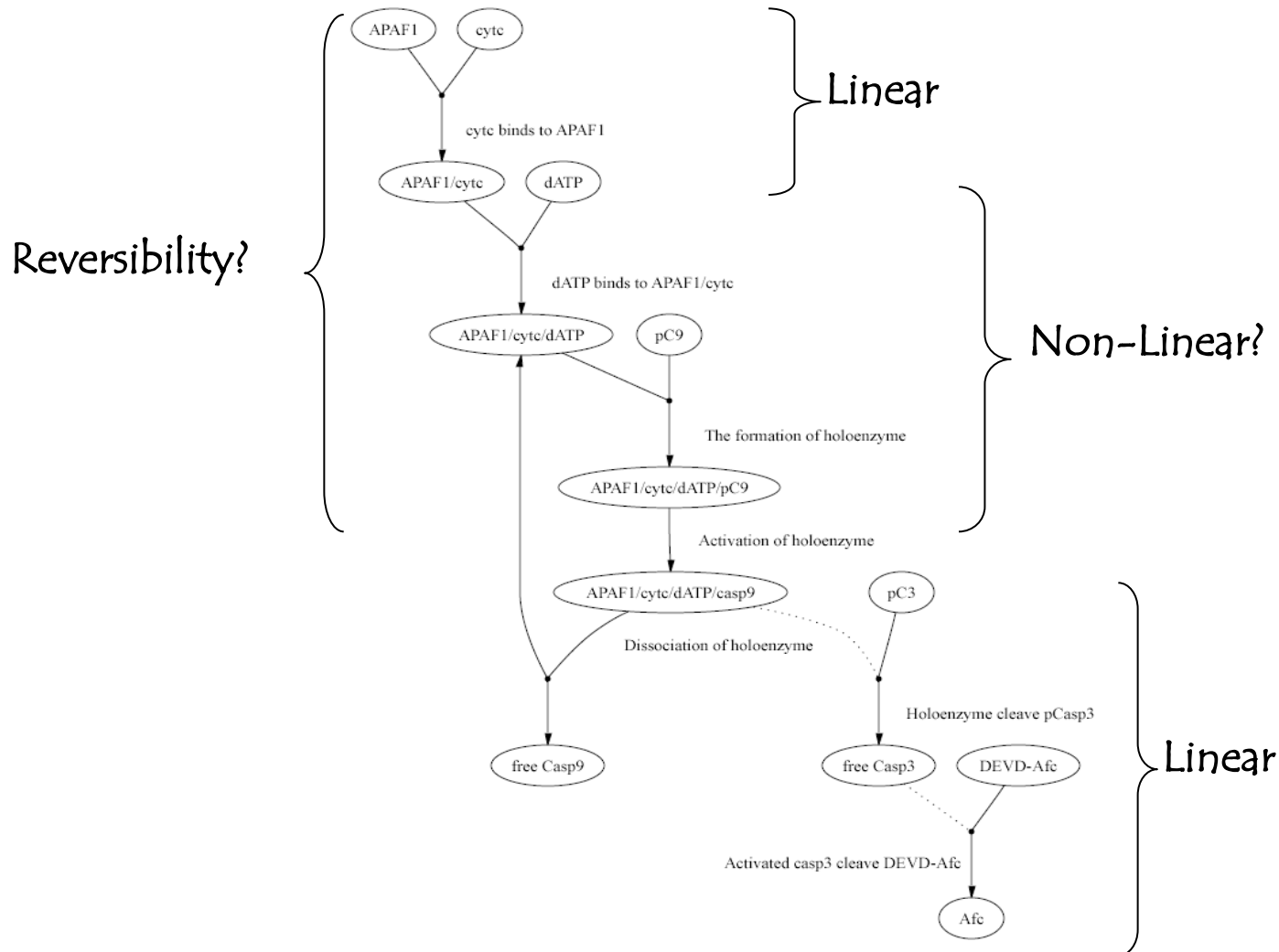


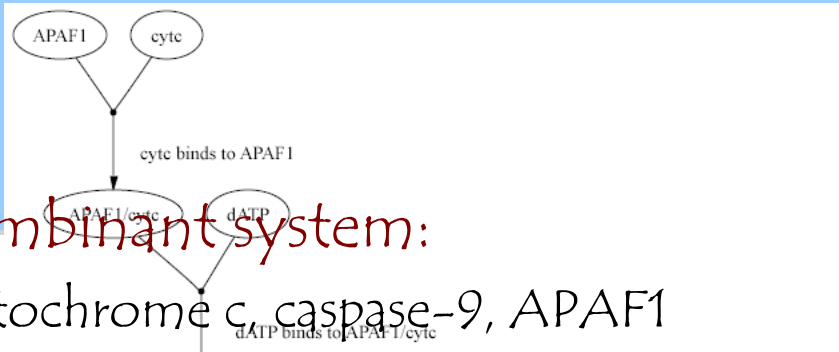
# Decreasing [APAF-1] Kill Caspase Activity

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# Where to modify the model in Simpathica?

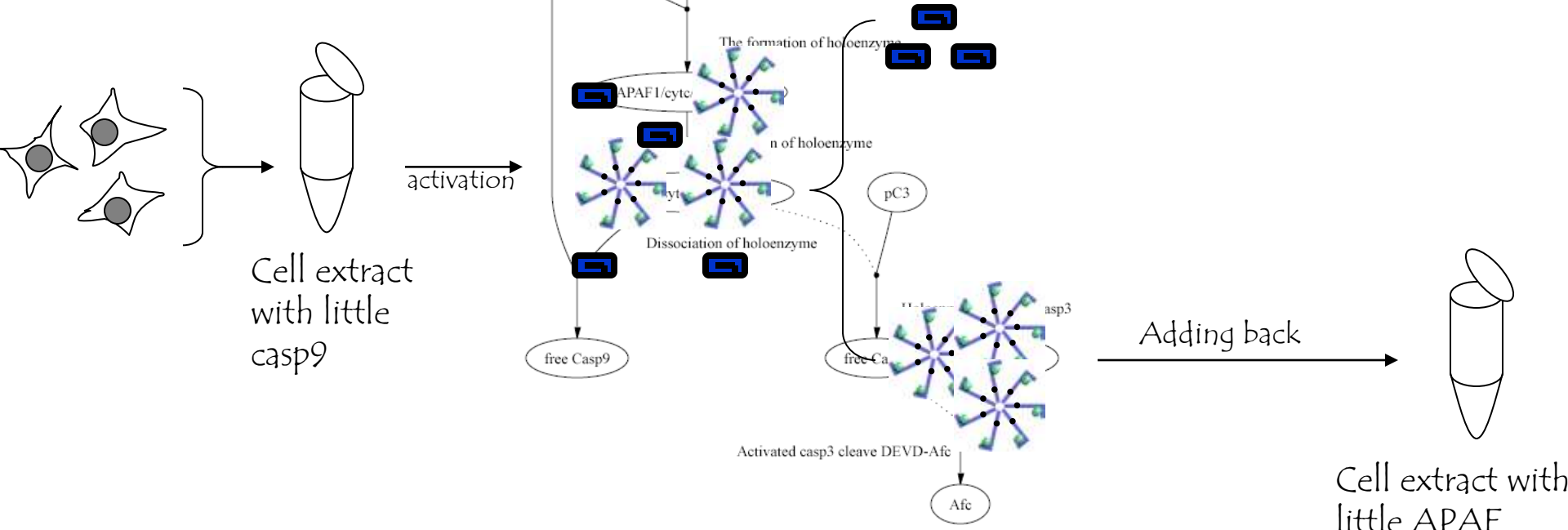




◆ Recombinant system:

- cytochrome c, caspase-9, APAF1

◆ Purification of endogenous APAF1/cytc oligomer



[APAF1/cytc/dATP] → caspase3 activity  
Linear dependence?

# XS-Systems:

(AAMC M. et al. 2001-2009)

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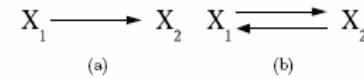


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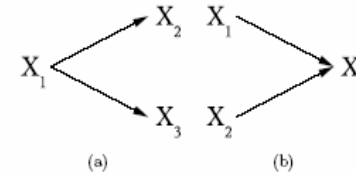


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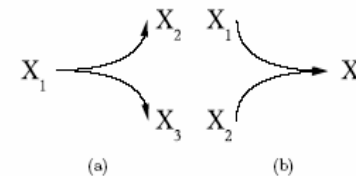


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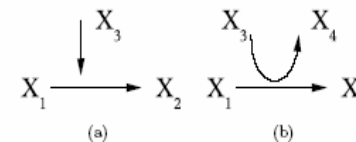


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# Formal Definition of S-system

**Definition 1 (S-system).** An S-system is a quadruple  $S = (DV, IV, DE, C)$  where:

- $DV = \{X_1, \dots, X_n\}$  is a finite non empty set of dependent variables ranging over the domains  $D_1, \dots, D_n$ , respectively;
- $IV = \{X_{n+1}, \dots, X_{n+m}\}$  is a finite set of independent variables ranging over the domains  $D_{n+1}, \dots, D_{n+m}$ , respectively;
- $DE$  is a set of differential equations, one for each dependent variable, of the form

$$\dot{X}_i = \alpha_i \prod_{j=1}^{n+m} X_j^{g_{ij}} - \beta_i \prod_{j=1}^{n+m} X_j^{h_{ij}}$$

with  $\alpha_i, \beta_i \geq 0$  called rate constants;

- $C$  is a set of algebraic constraints of the form

$$C_j(X_1, \dots, X_{n+m}) = \sum (\gamma_j \prod_{k=1}^{n+m} X_k^{f_{jk}}) = 0$$

with  $\gamma_j$  called rate constraints.

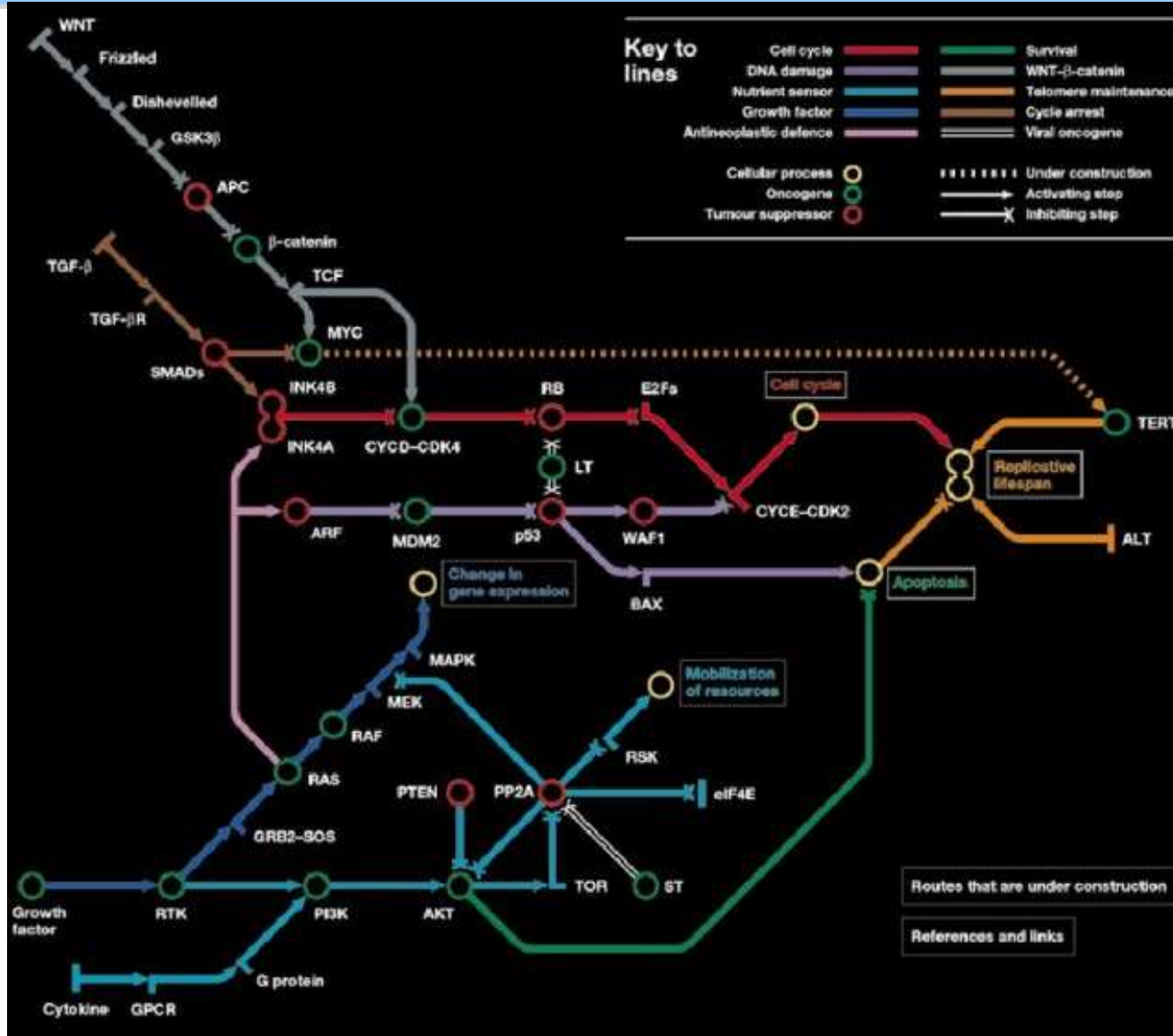
# Verifying temporal properties of a reactive system

- Step 1.** Formally encode the behavior of the system as a semi-algebraic hybrid automaton
- Step 2.** Formally encode the properties of interest in TCTL
- Step 3.** Automate the process of checking if the formal model of the system satisfies the formally encoded properties using quantifier elimination

# Solution

- Bounded Model Checking
- Constrained Systems
  - Linear Systems
  - O-minimal
  - SACoRe (Semi algebraic Constrained Reset)
  - IDA

# Subway Map of Cancer





# Is this View of Cancer Necessarily Accurate ?

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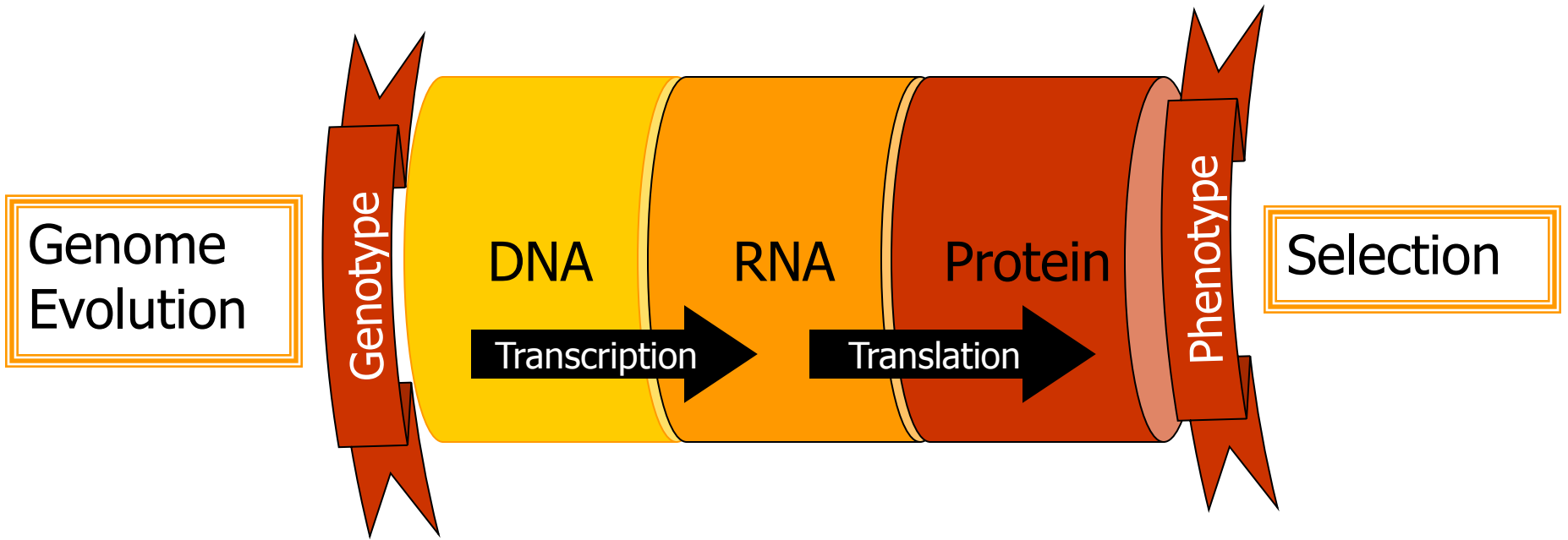


- “If I said **yes**, that would then suggest that that might be the only place where it might be done which would **not be accurate, necessarily accurate.**
- “**It might also not be inaccurate, but I'm disinclined to mislead anyone.**”
  - *Ex-US Secretary of Defense, Mr. Donald Rumsfeld, Once again quoted completely out of context.*

# Known Unknown Biology

- Reality: “World Where There Are No Names of Anything.”

# The New Synthesis



# Cancer Initiation and Progression

**Mutations, Translocations,  
Amplifications, Deletions**

**Epigenomics (Hyper & Hypo-  
Methylation)**

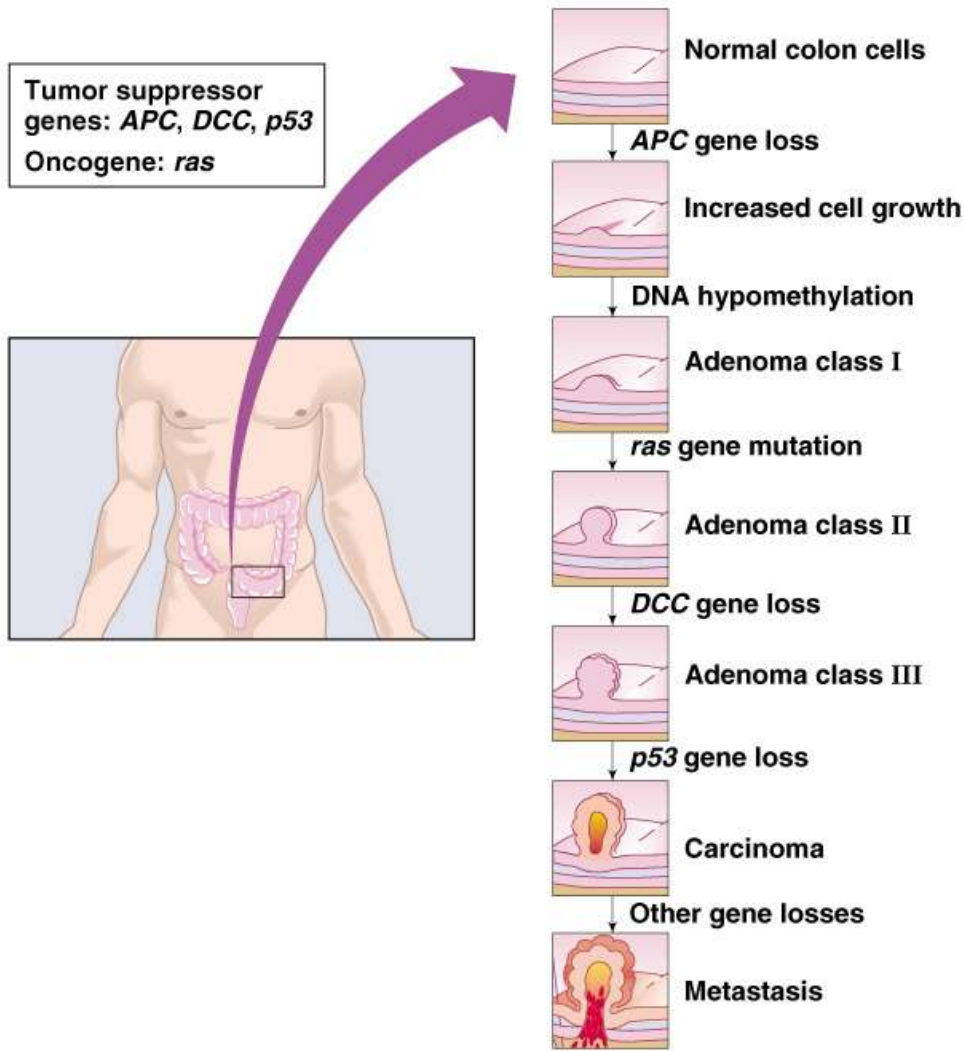
**Alternate Splicing**

Cancer Initiation and Progression



**Proliferation, Motility,  
Immortality,  
Metastasis, Signaling,  
Microenvironment  
(autophagy)**

# Amplifications & Deletions



Mutation in a TSG

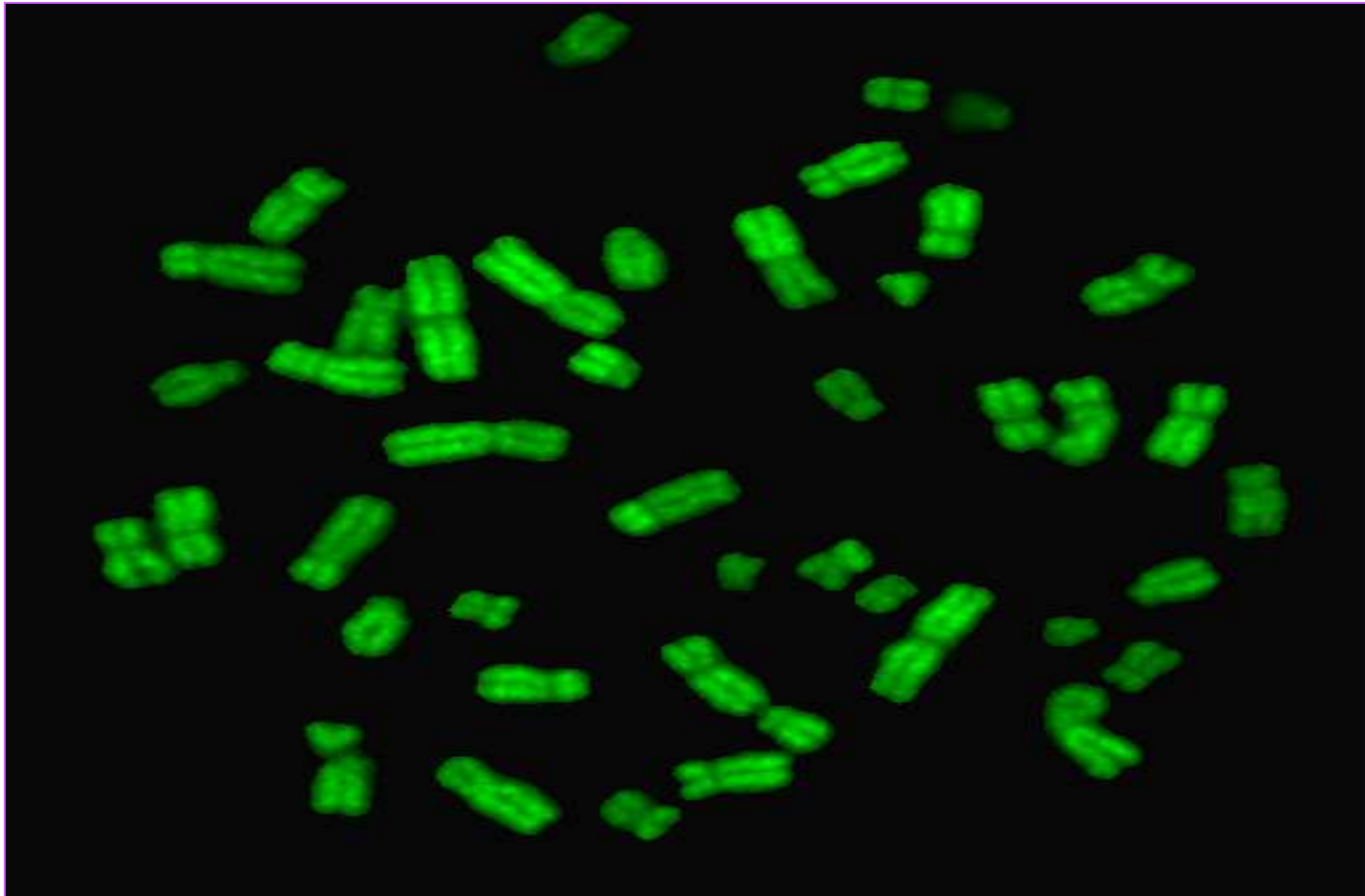
Epigenomics

Conversion of a Proto-Oncogene

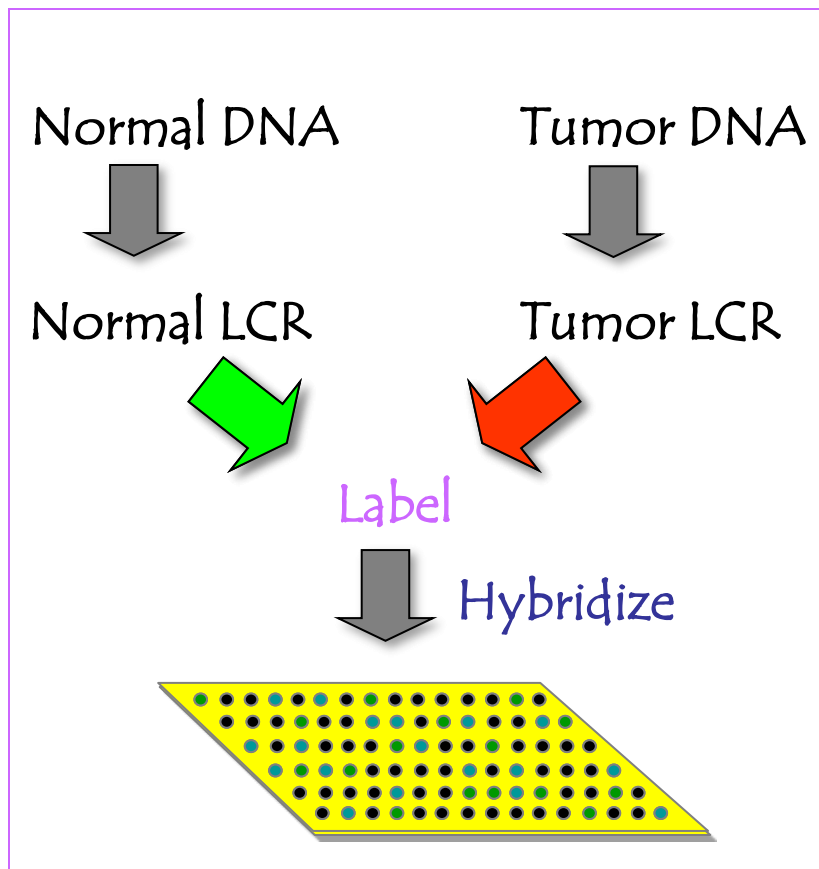
Deletion of a TSG

Deletion of a TSG

# Karyotyping

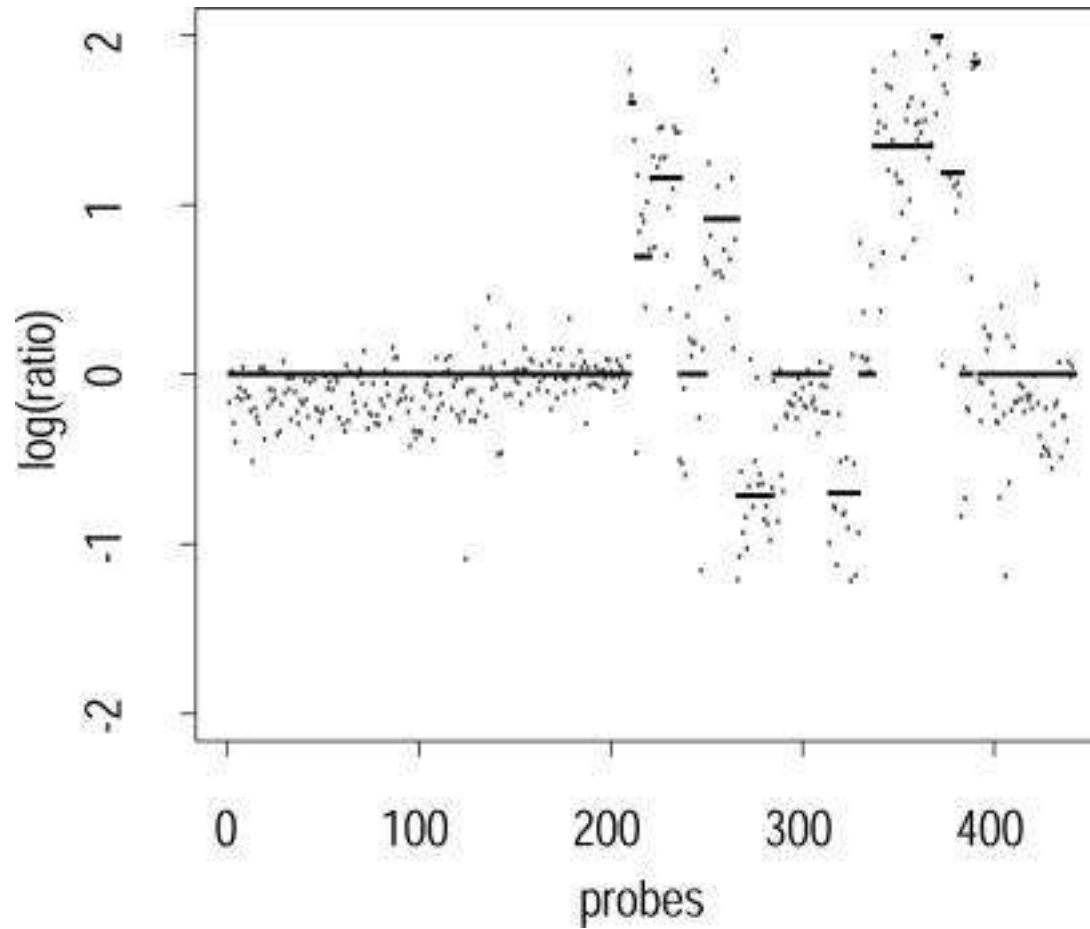


# Microarray Analysis of Cancer Genome



- Representations are reproducible samplings of DNA populations in which the resulting DNA has a reduced complexity.
  - Array probes derived from low complexity representations of the normal genome
  - We measure differences in gene copy number between normal and tumor samples ratiometrically

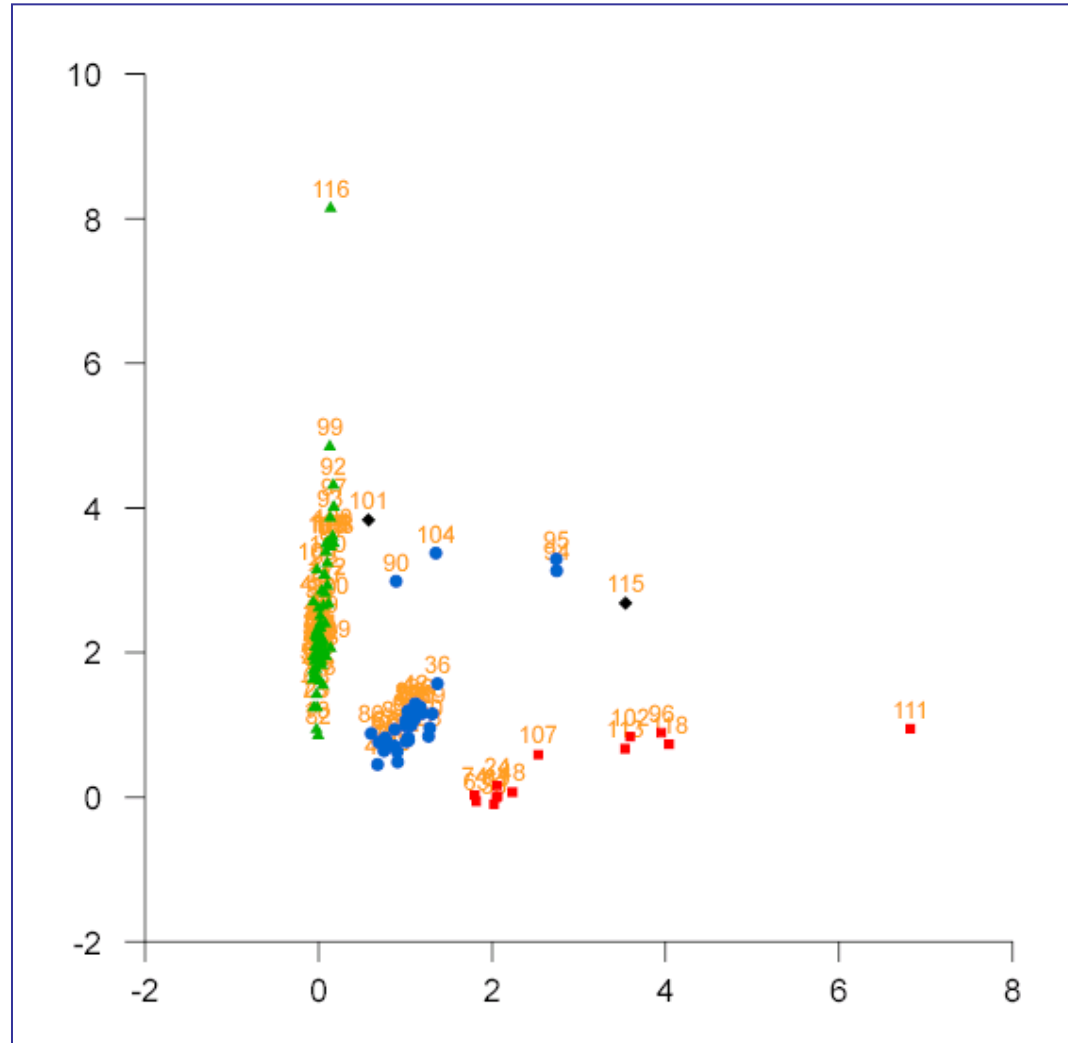
# Daruwala et al. (PNAS, 2004)





# Allelic Frequencies: Cancer & Normal

(Anantharaman et al. unpublished)



# Cell Stress: Glycosylation

- Some tumor-specific conditions (e.g., hypoxia, low pH and low level of glucose) commonly cause the glucose-regulated stress response of cancer cells.
- One can induce various stress responses in cancer cells artificially, and study them experimentally.
- For example, Tunicamycin induces (glycosylation) stress:
  - It blocks the synthesis of all N-linked glycoproteins (N-glycans)
  - And causes cell cycle arrest in G1 phase.

- Proprietary experimental results removed.

# Concept

(M. et al. 2006-2009)

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PolyA cDNAs in solution



Shear Flow

cDNAs fixed to surface



Restriction Enzyme ex. '*Rsa I*'



cDNAs 'coded'  
ex. '*GTAC*'



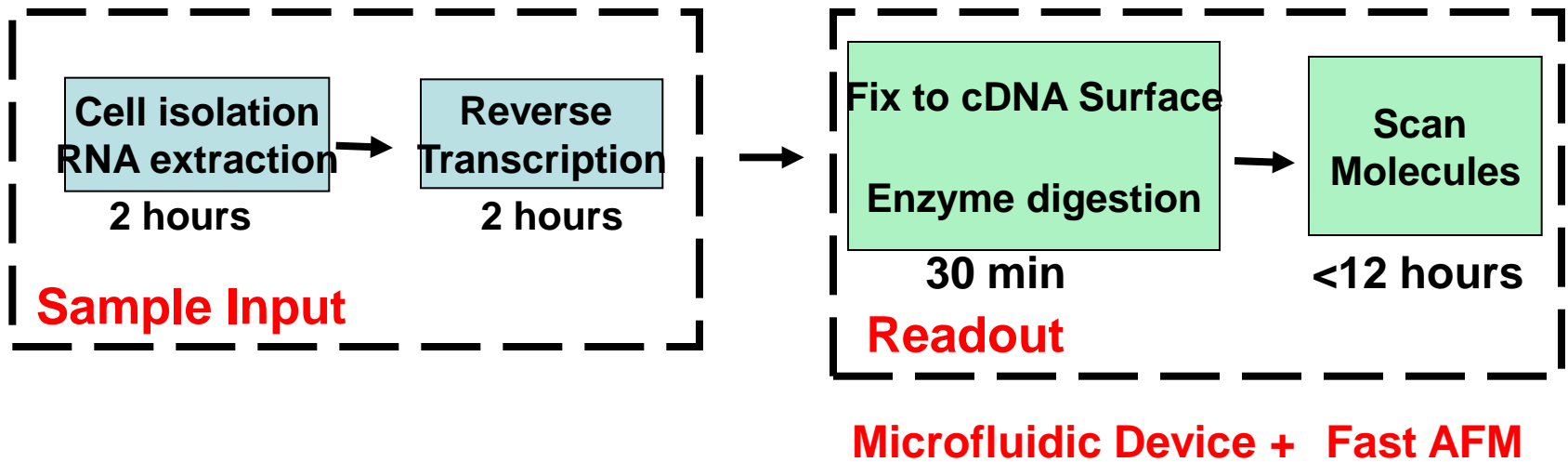
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AFM Imaging

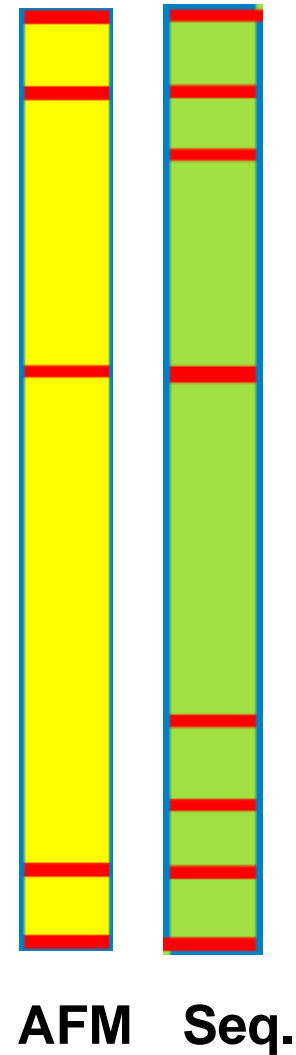
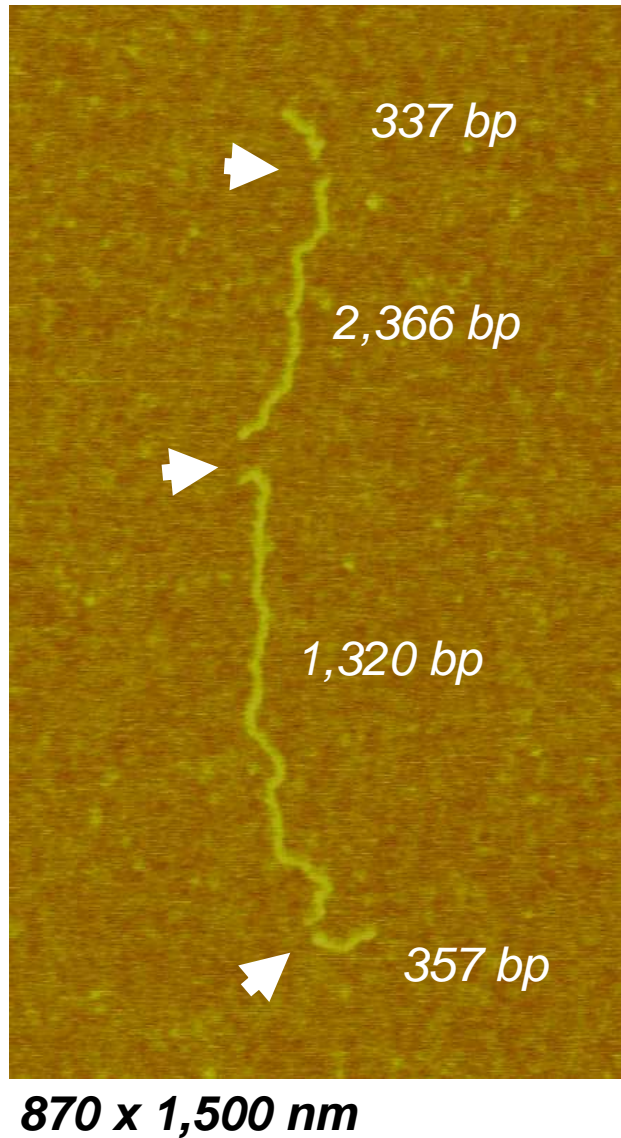


Image Processing, Pattern Matching

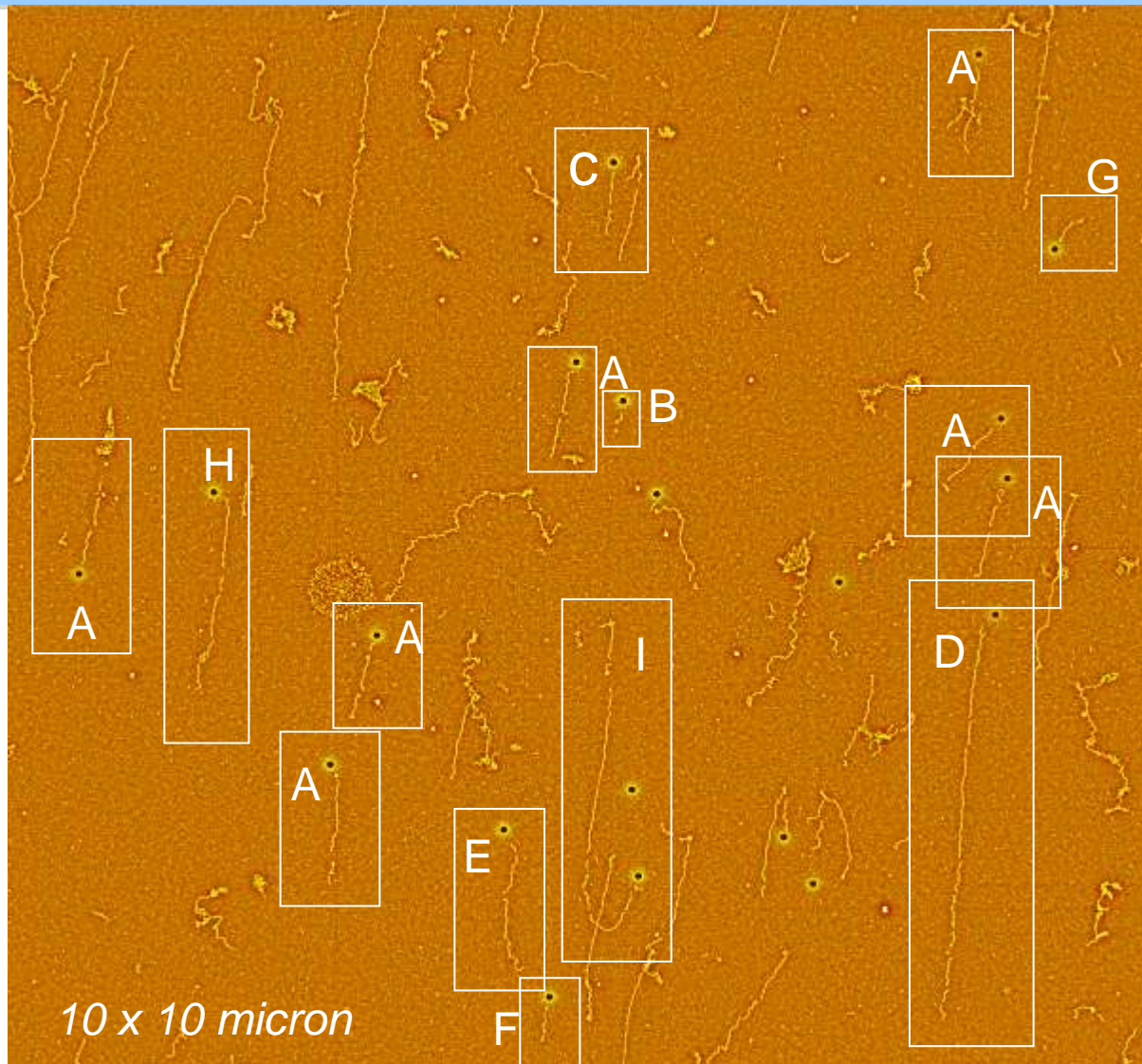
# Single Molecule Restriction Map



# AFM vs Sequence

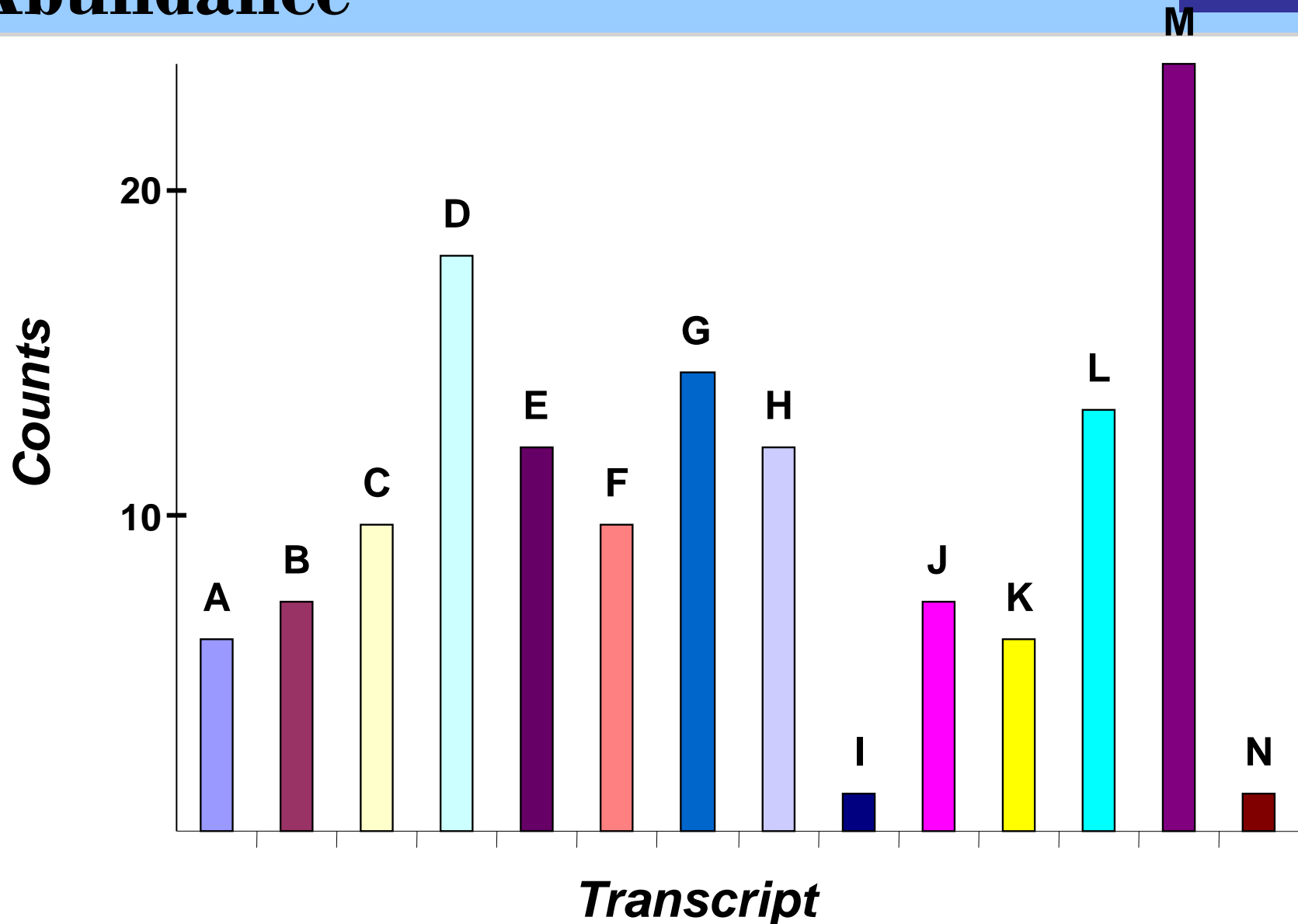


# Identify and Count



# Histogram of Transcript Abundance

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# Models that are Concepty



- “I’m not into this detail stuff.
- “I’m more concepty.”
  - *Ex-US Secretary of Defense, Mr. Donald Rumsfeld, Once again quoted completely out of context.*

# GOALIE: GO Algorithmic Logic for Invariant Extraction

The screenshot displays a software interface with several panels:

- Source cluster:** A table with columns 'Accessi...' and 'GO Categories'. It lists various GO terms and their associated IDs.
- Edge cover:** A table with columns 'Description' and 'Becomes true'. It lists biological processes like 'skeletal development' and 'energy pathways'.
- Becomes true:** A table with columns 'Description', 'GO Term', and 'Description'. It lists GO terms like 'GO:0006873' and 'GO:0007160'.
- GO Term / Description:** A table at the bottom left listing GO terms and their descriptions.

Red arrows point from blue callout boxes to specific rows in the 'Edge cover' and 'Becomes true' tables:

- Arrow 1 points to the row for 'GO:0006873' in the 'Becomes true' table.
- Arrow 2 points to the row for 'GO:0007160' in the 'Becomes true' table.
- Arrow 3 points to the row for 'GO:0006873' in the 'Edge cover' table.
- Arrow 4 points to the row for 'GO:0007160' in the 'Edge cover' table.

GO categories describing genes in "source" cluster

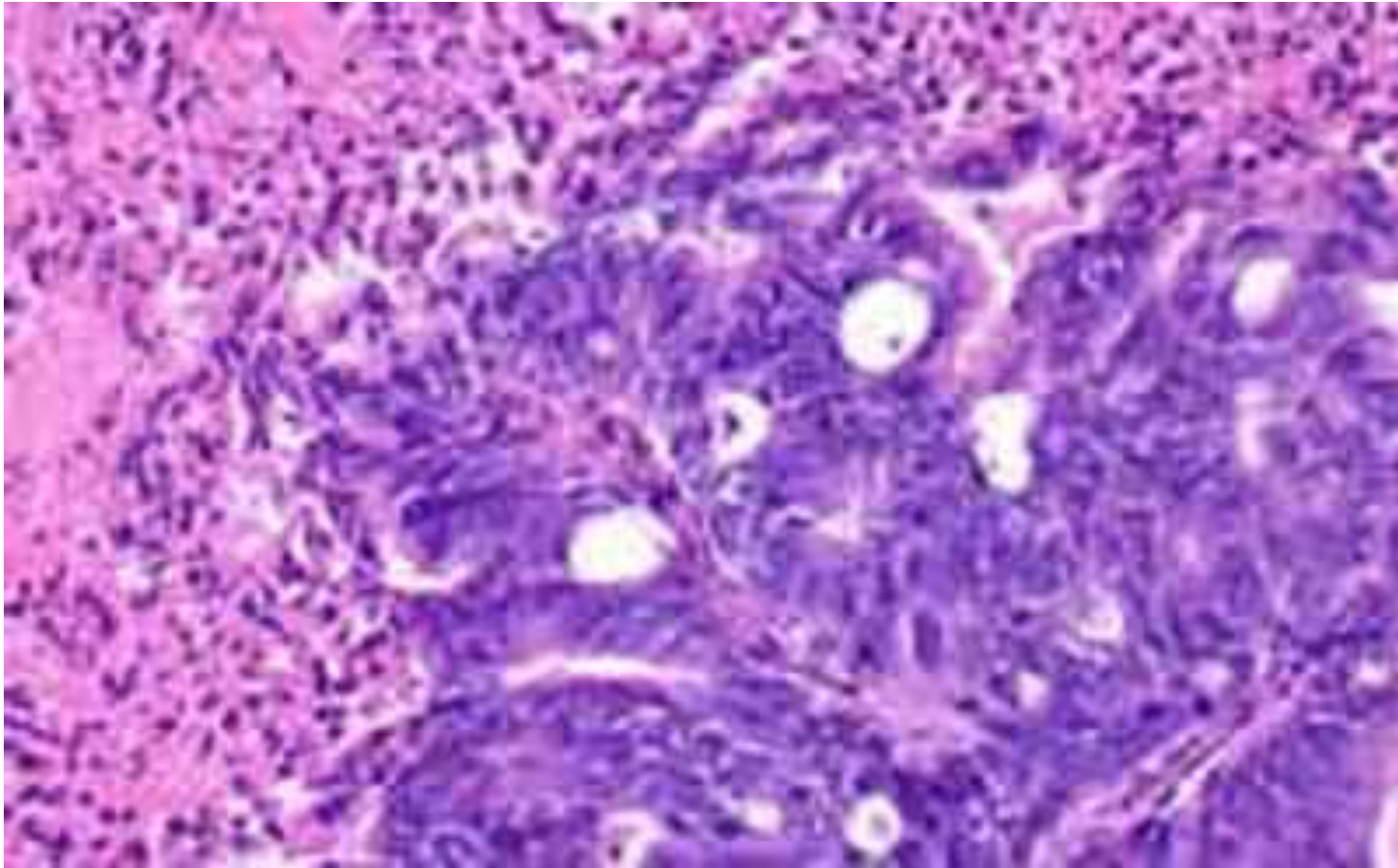
GO categories shared with "destination" cluster

GO categories describing "destination" cluster but not "source"

GO categories describing "source" cluster but not "destination"

# Unknown Unknown Biology

# Pathologist's View



*Healthy and diseased pancreas cells*

# A Challenge

- **“At present, description of a recently diagnosed tumor in terms of its underlying genetic lesions remains a distant prospect. Nonetheless, we look ahead 10 or 20 years to the time when the diagnosis of all somatically acquired lesions present in a tumor cell genome will become a routine procedure.”**
  - Douglas Hanahan and Robert Weinberg
    - *Cell*, Vol. **100**, 57-70, 7 Jan 2000



# Blast from the Past



- **“I would not say that the future is necessarily less predictable than the past. I think the past was not predictable when it started.”**
  - *Ex-US Secretary of Defense, Mr Donald Rumsfeld.*

- Measurements
  - Single Cell Single Molecule Experiments
- Modeling & Model Checking
  - Phenomenological & Mechanistic Models
- Mining
  - Hypotheses
- Manipulation
  - Diagnostics and Therapeutics

# Translational Systems Biology

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# Answer to Cancer



- **“If I know the answer I'll tell you the answer, and if I don't, I'll just respond, cleverly.”**
  - *Ex-US Secretary of Defense, Mr. Donald Rumsfeld.*



**The end**