A Collaborative Proposal to the NSF Experimental Expeditions Program

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Computational Biology of Cancer

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Carnegie Mellon · NASA · Stony Brook State University of New York · University of Maryland · Lehman College · NYU New York University · Cornell University Founded A.D. 1865 · University of Pittsburgh

Our Vision

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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

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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

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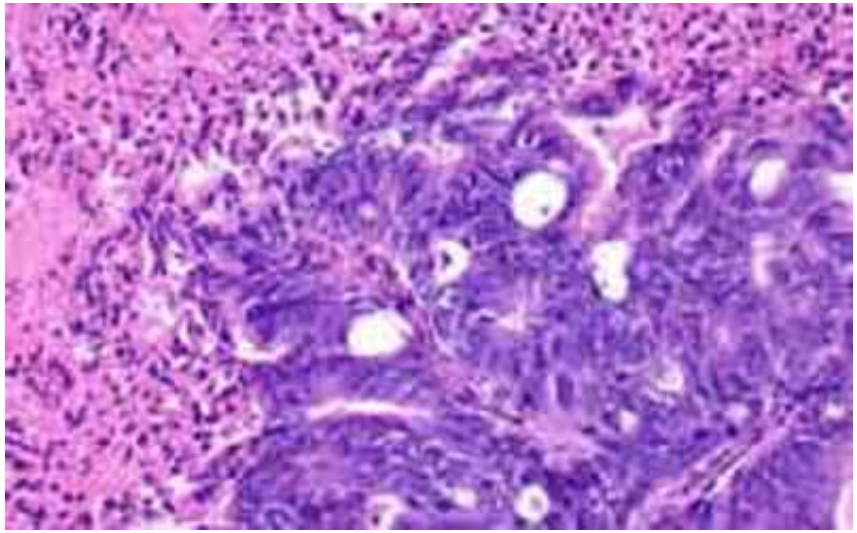
- 4th leading cause of cancer death in the US and Europe
- Five-year survival rate is only 4%
- Almost no progress in diagnosis and treatment in the past 40 years



Healthy and diseased pancreas cells

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

Why Pancreatic Cancer?

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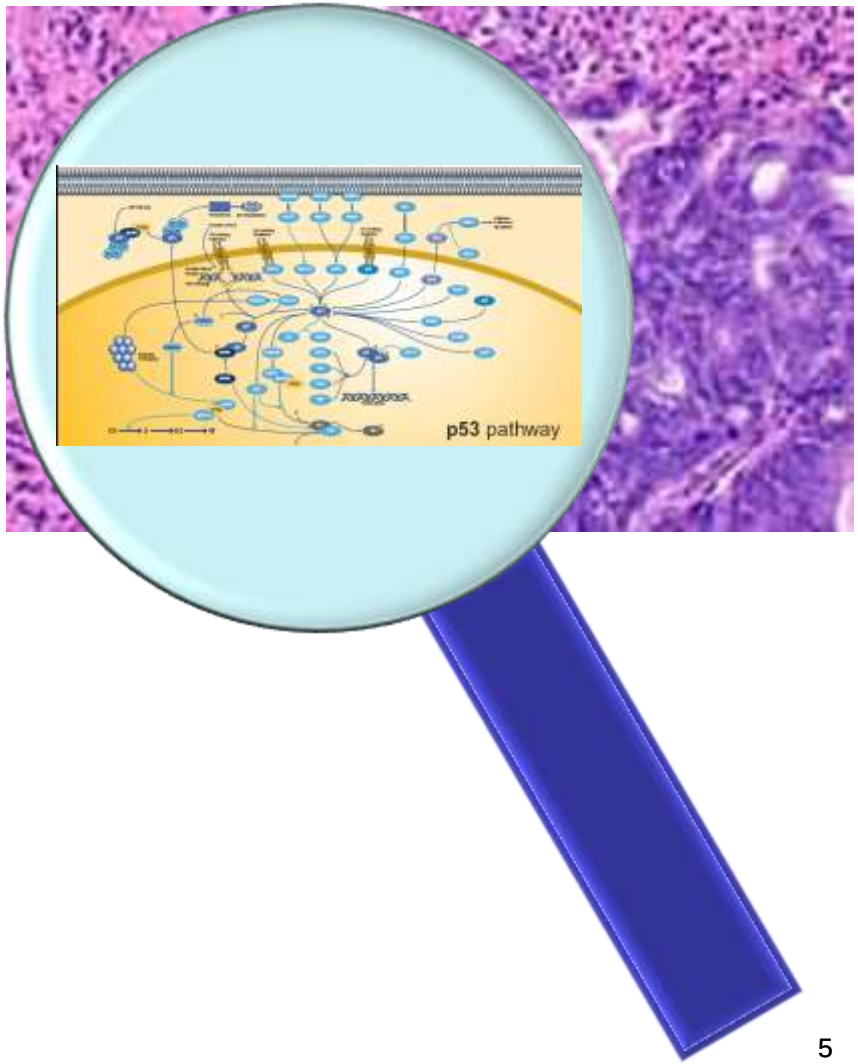
- No animal model, so computational models are needed
- Signaling models from cancer experts at **TGEN** (Translational Genomics)
- We will build new analysis and verification tools
- TGEN collaborators will use tools to better understand cancer dynamics



Model Checking

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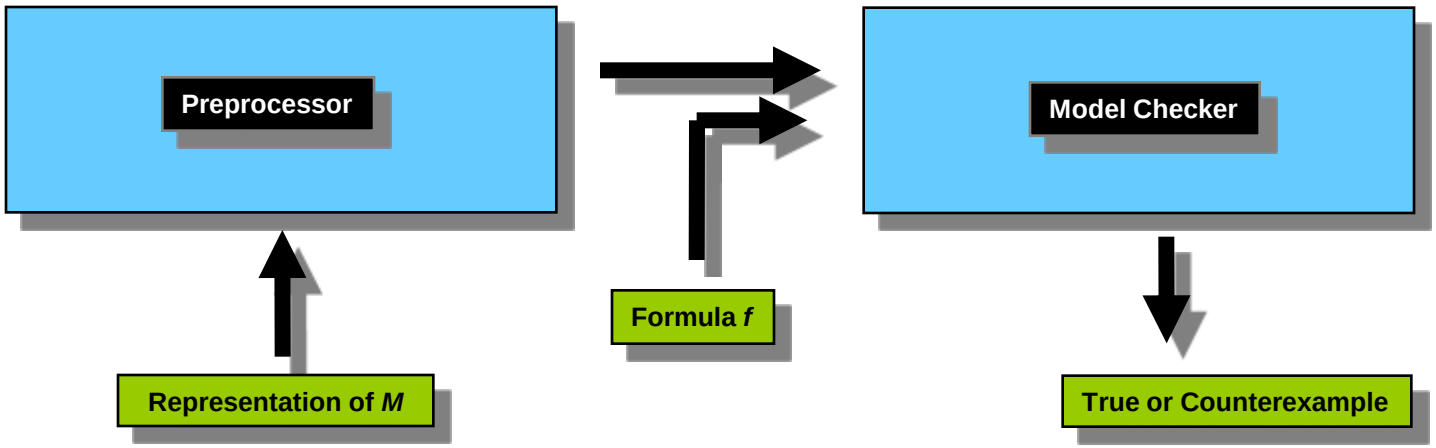
The **Model Checking Problem**:

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

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

e.g., a U b means "**a** holds true Until **b** becomes true"

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



Biological Models of Cancer

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- 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

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

War on Cancer

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- "… 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

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

“Addicted to Death”

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- 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

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- **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

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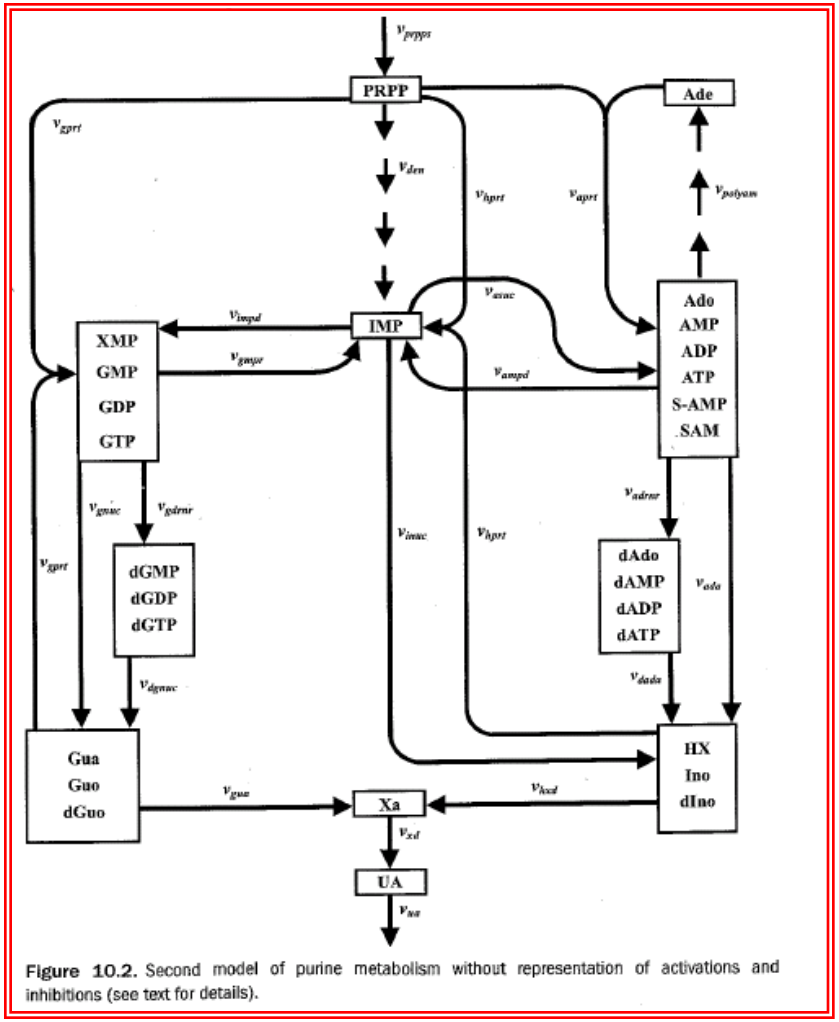

Figure 10.2. Second model of purine metabolism without representation of activations and inhibitions (see text for details).

Biochemistry of Purine Metabolism

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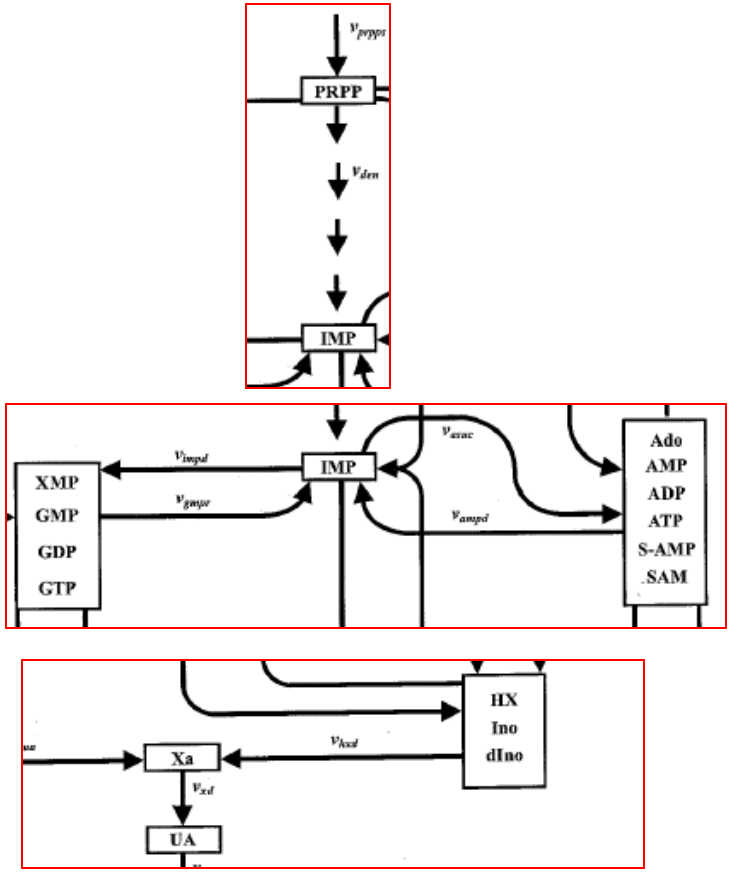

- The main metabolite in purine biosynthesis is *5-phosphoribosyl-a-1-pyrophosphate* (*PRPP*).
  - A linear cascade of reactions converts PRPP into *inosine monophosphate* (*IMP*).
  - IMP is transformed into AMP and GMP.
  - Guanosine, adenosine and their derivatives are recycled (unless used elsewhere)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

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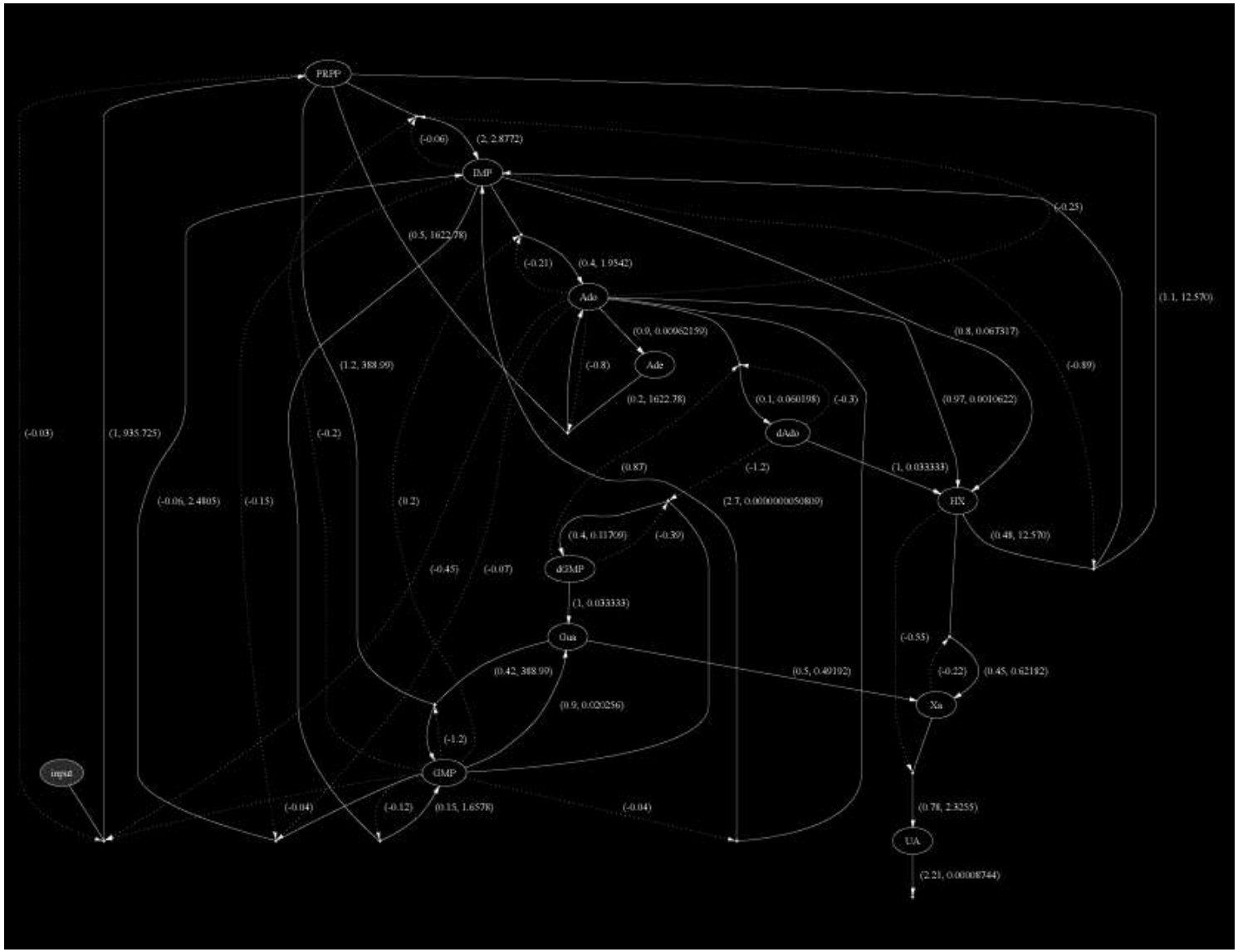
Purine Metabolism



Queries

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- Variation of the initial concentration of PRPP does not change the steady state. **(PRPP = 10 * PRPP1) implies steady_state()**

TRUE

- 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

Queries

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- 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

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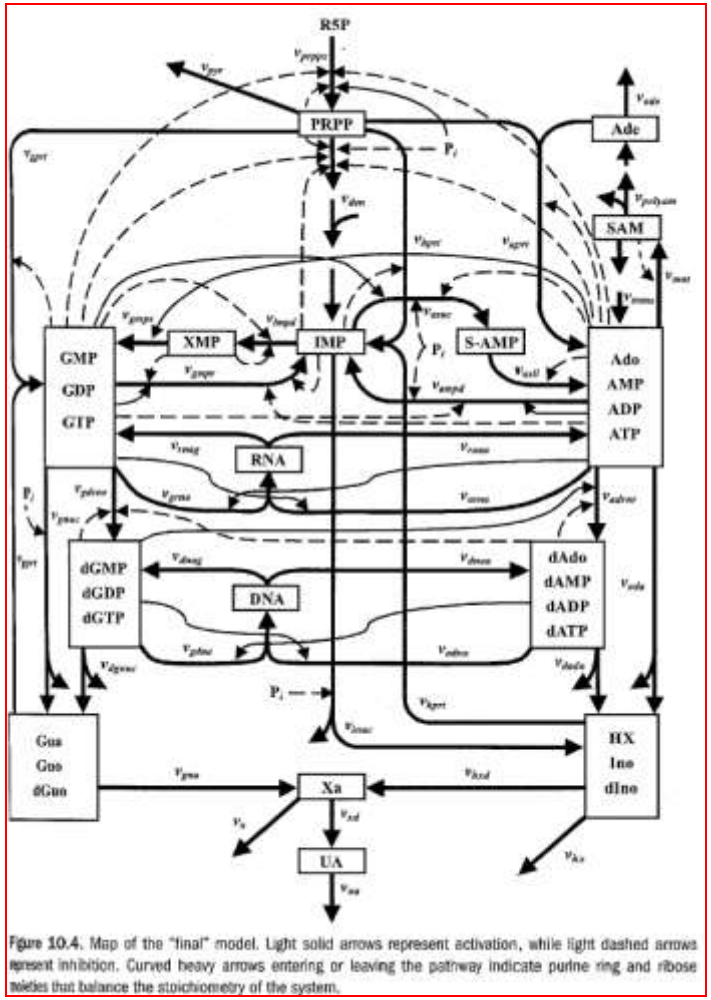

Figure 10.4. Map of the "final" model. Light solid arrows represent activation, while light dashed arrows represent inhibition. Curved heavy arrows entering or leaving the pathway indicate purine ring and ribose moieties that balance the stoichiometry of the system.

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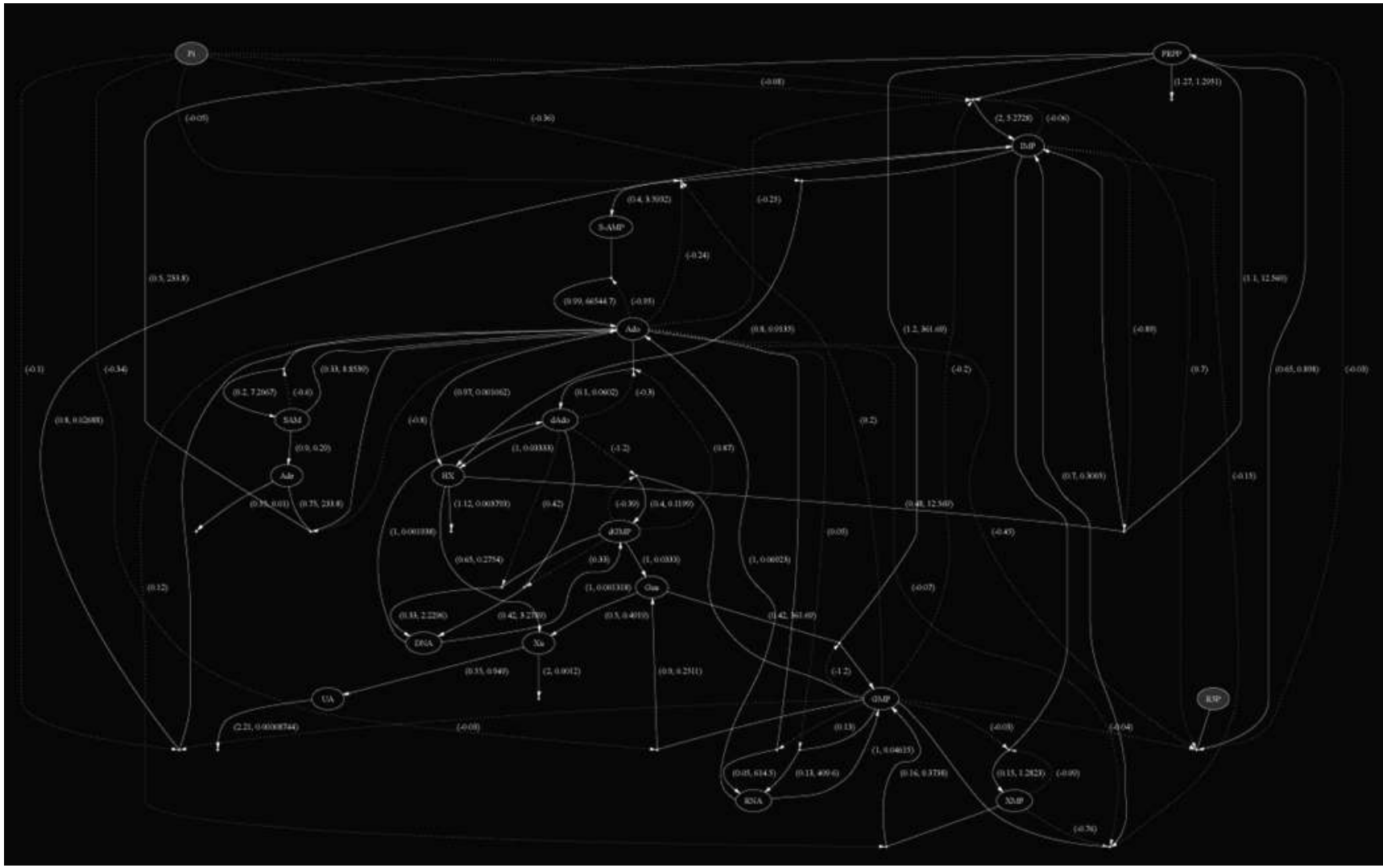
Purine Metabolism



XS-Systems:
(AAMC M. et al. 2001-2009)

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Canonical Form:

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

Characteristics:

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

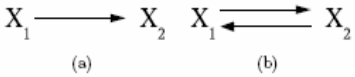

Figure 1: Representation of an unmodified and of a reversible reaction.

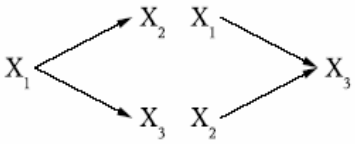

Figure 2: Representation of a divergence and of a convergence branch point (the two processes in each reaction are independent of each other).

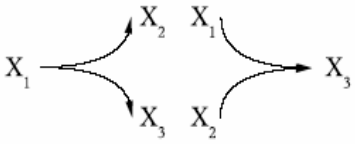

Figure 3: Representation of a single splitting reaction generating two products, X_2 and X_3, in stoichiometric proportions and of a single synthetic reaction involving two source components, X_1 and X_2 always in stoichiometric proportions.

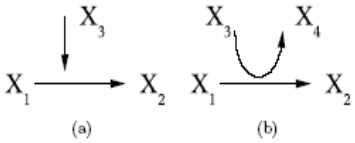

Figure 4: The conversion of X_1 into X_2 is modulated (stimulation or inhibition is represented by the sign of the arrow) by X_3. The reaction between X_1 and X_2 requires coenzyme X_3, which in the process is converted into X_4.

Rule-based modeling protocol

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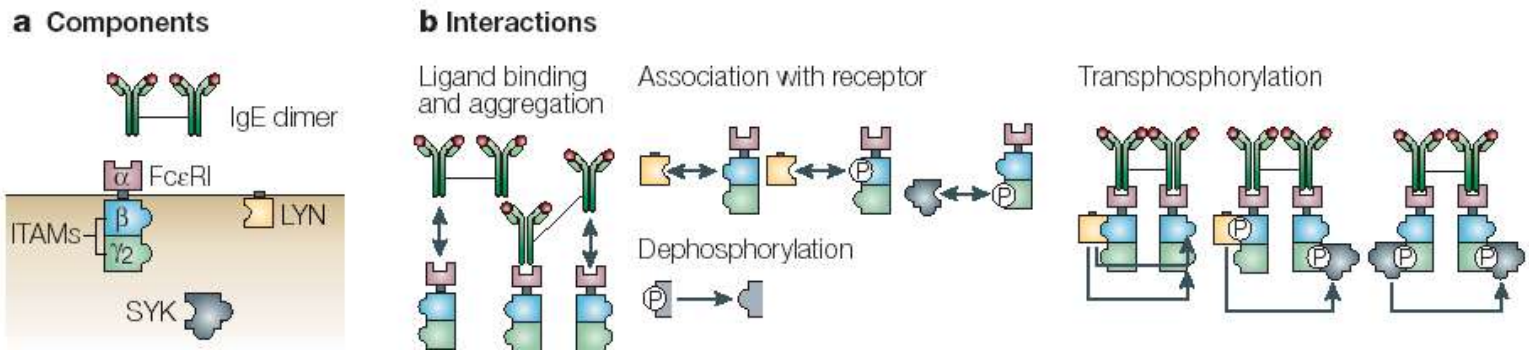
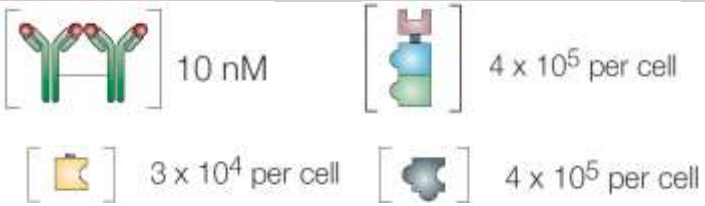
1. Define components as *structured objects* and interactions as *rules*.



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



3. Generate and simulate the model.

The activation of Casp9 needs APAF1 and cytochrome c

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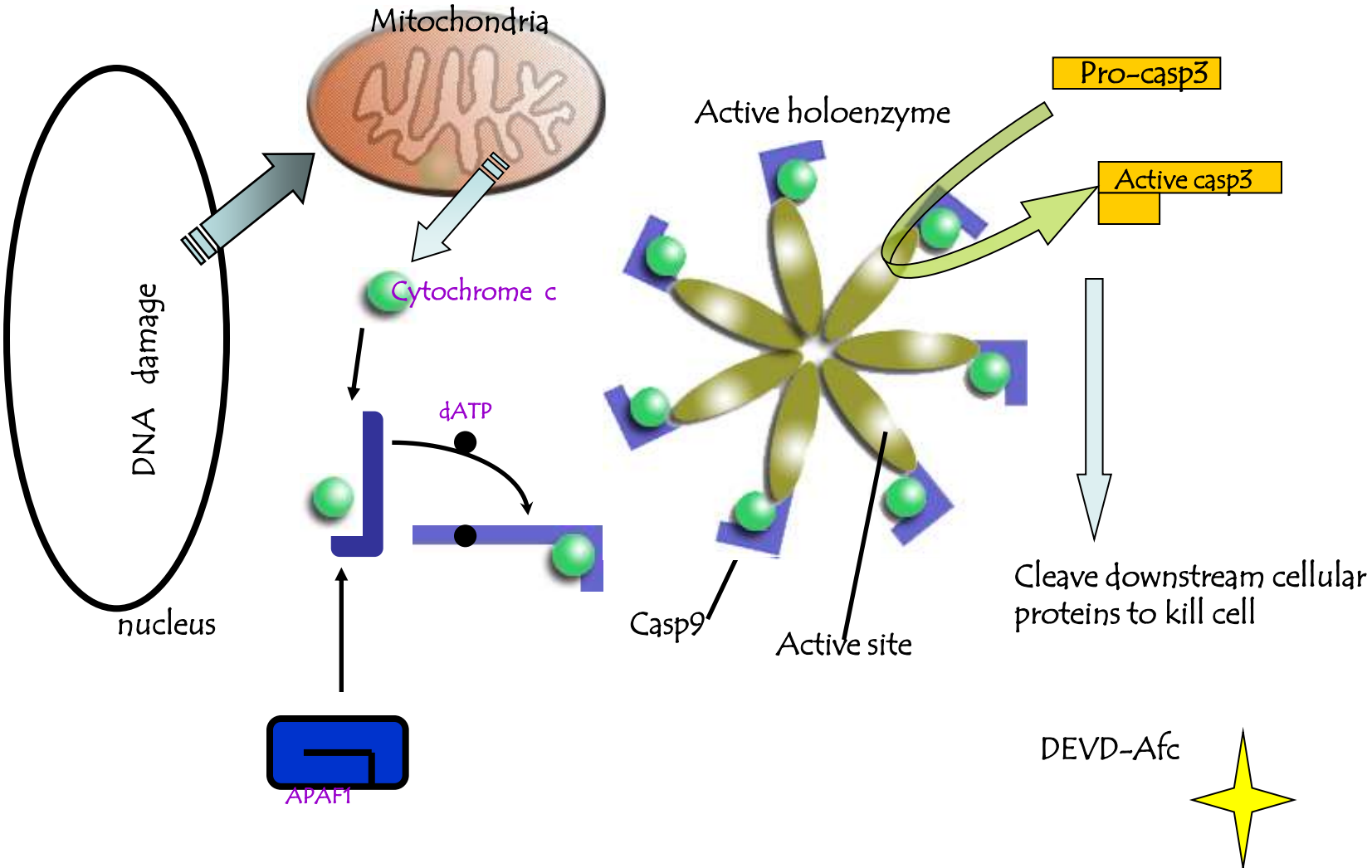

xS-System Model

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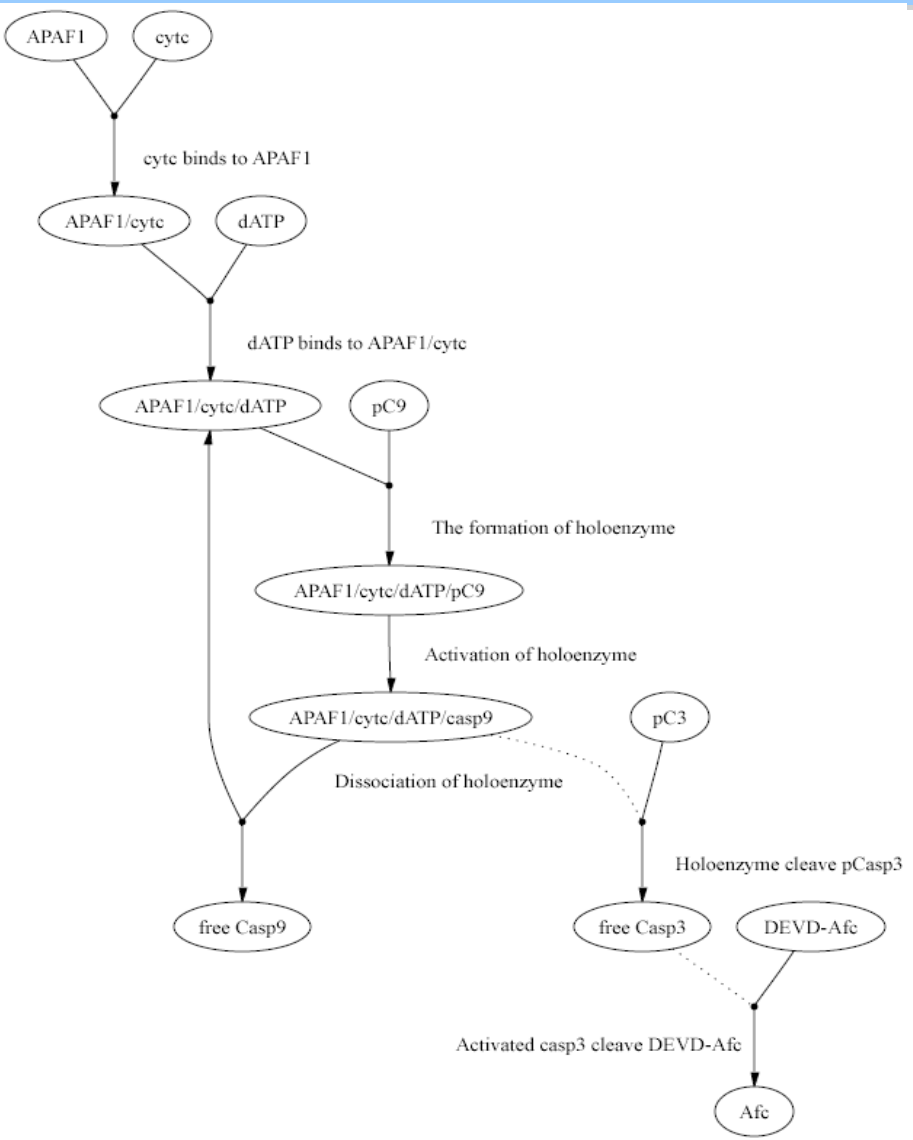

Simpathica recapitulate the holoenzyme formation process

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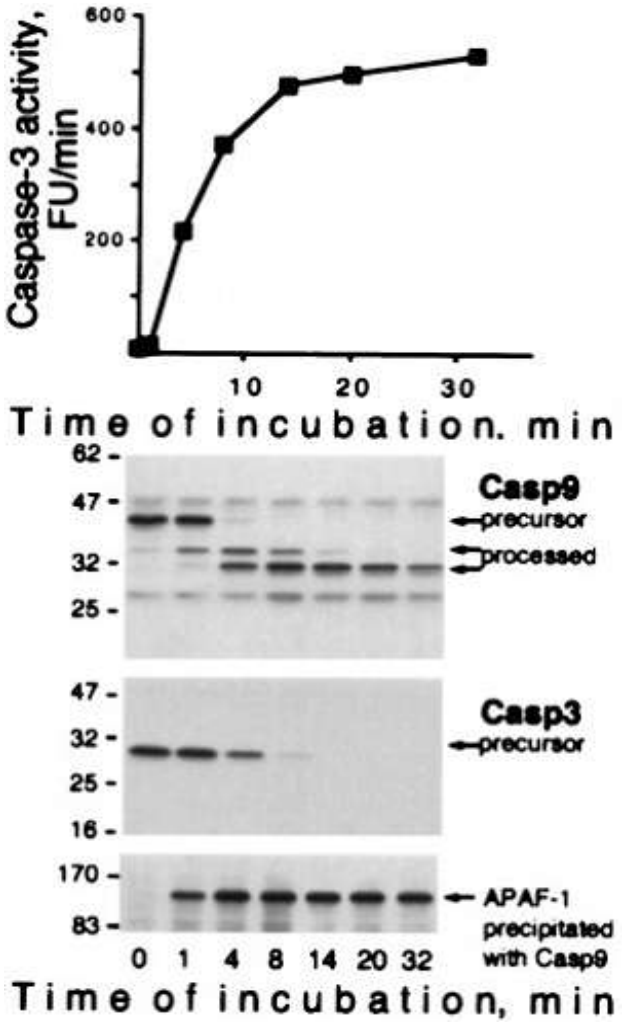

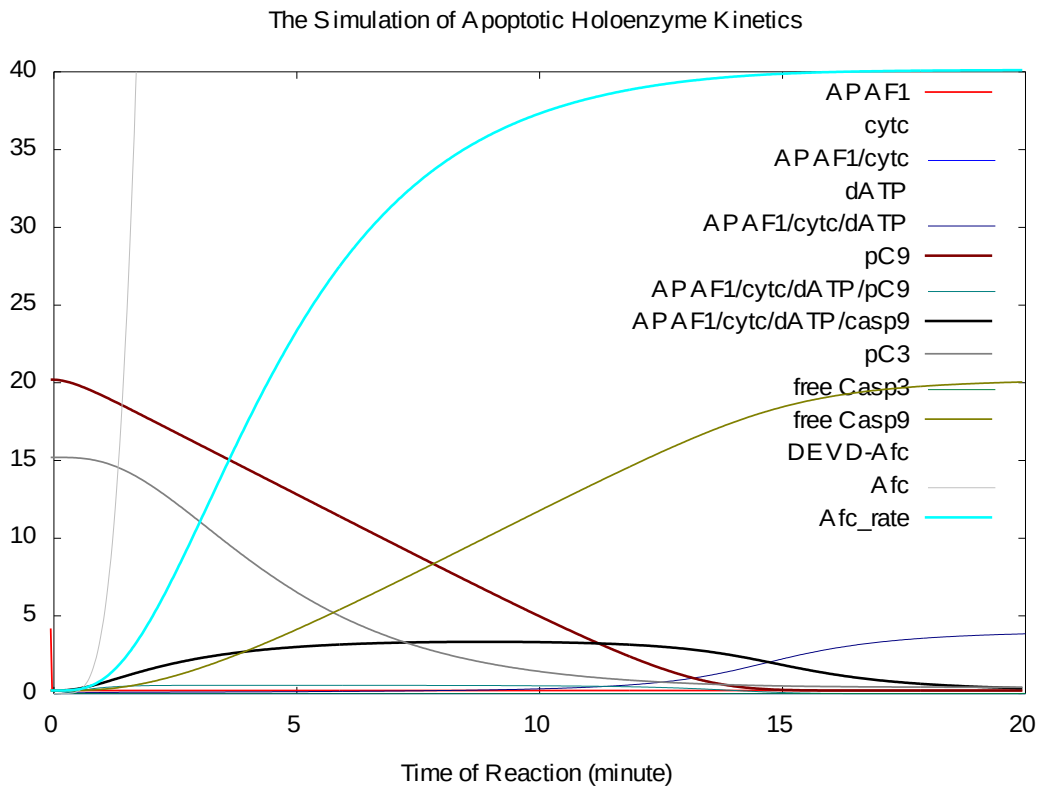

Rodriguez and Lazebnik (1999)

Decreasing [APAF-1] Kill Caspase Activity

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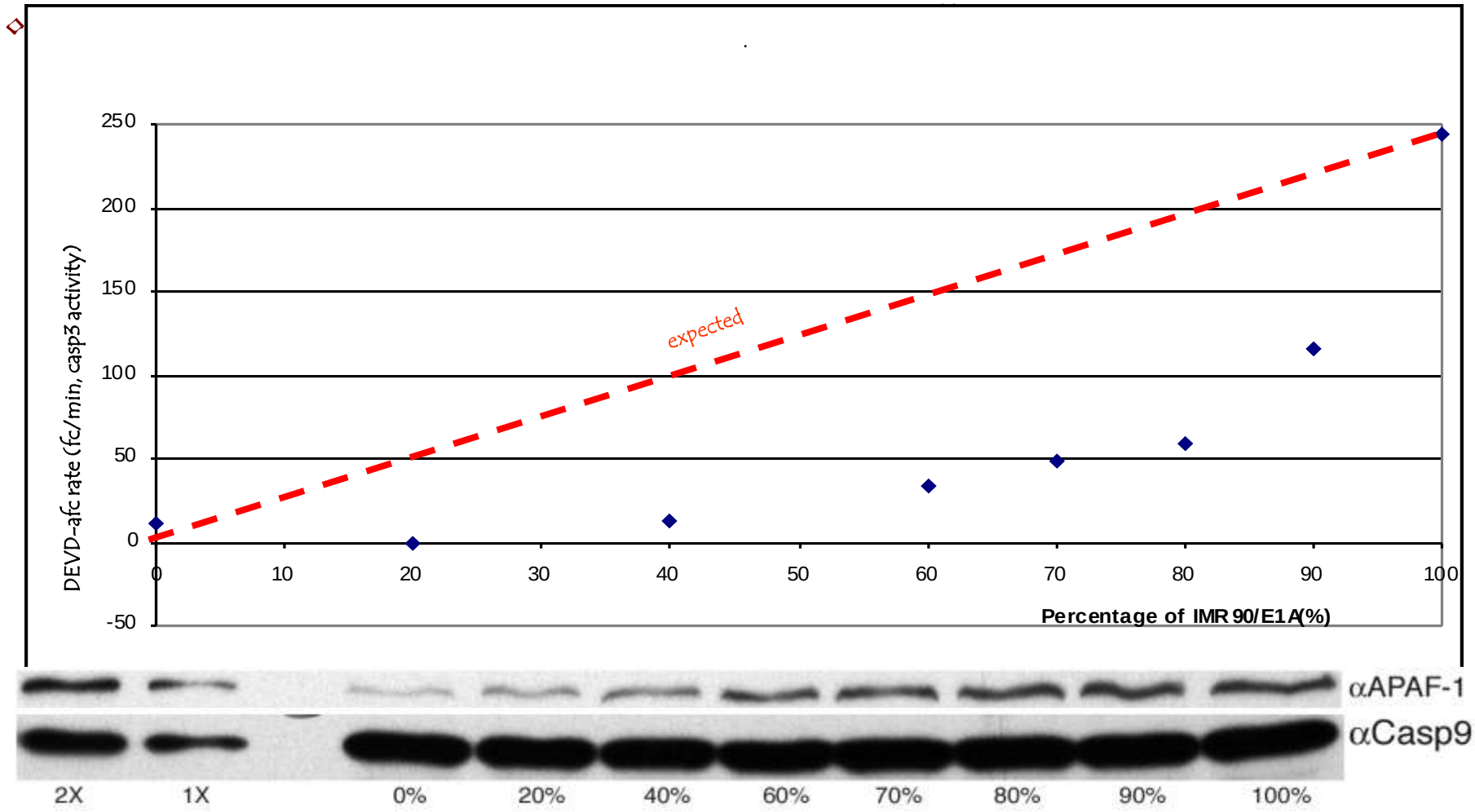

Where to modify the model in Simpathica?

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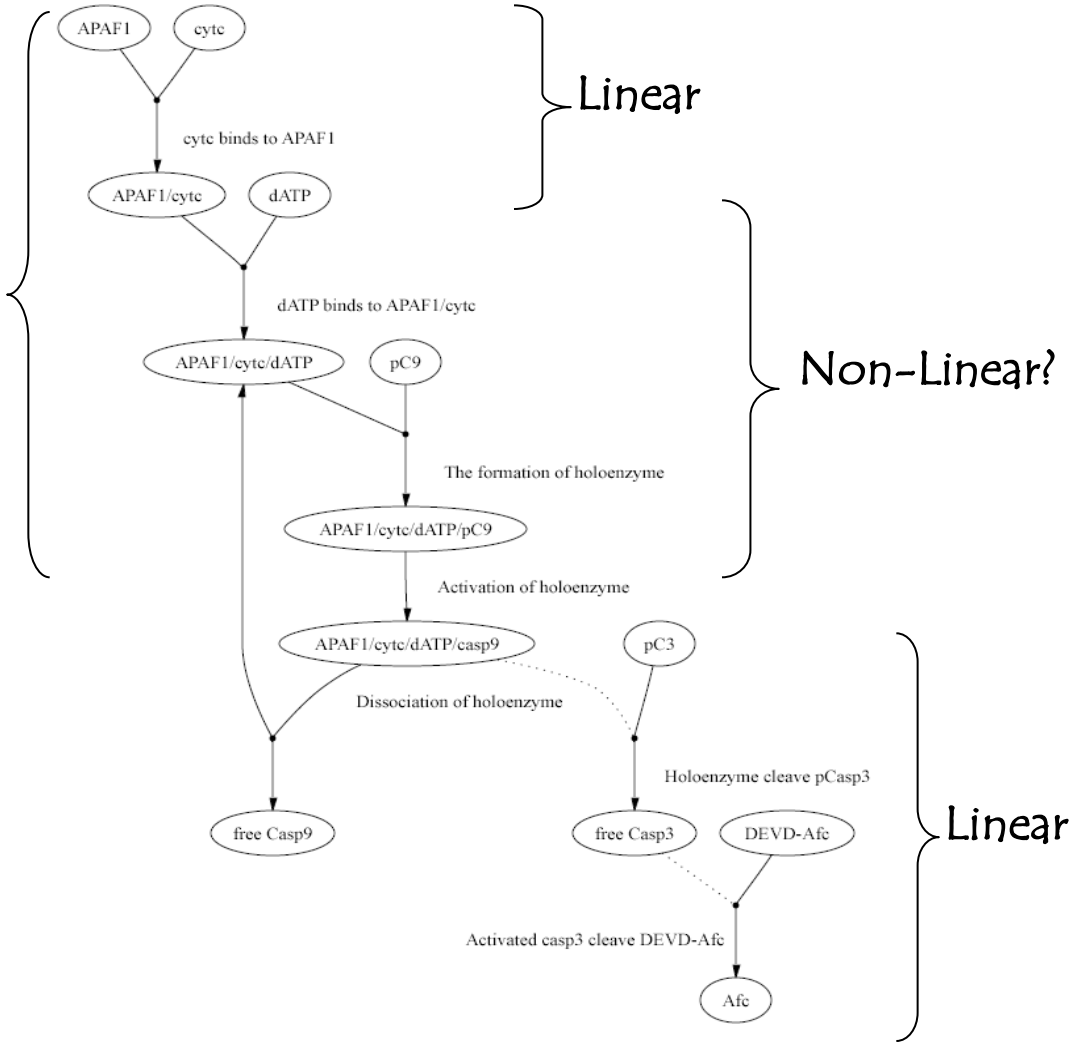
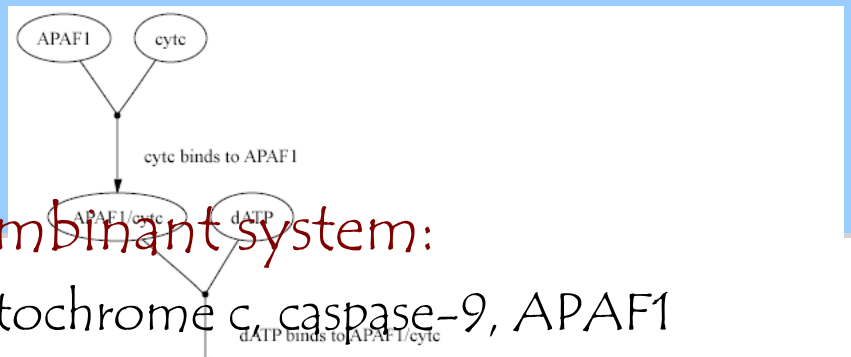
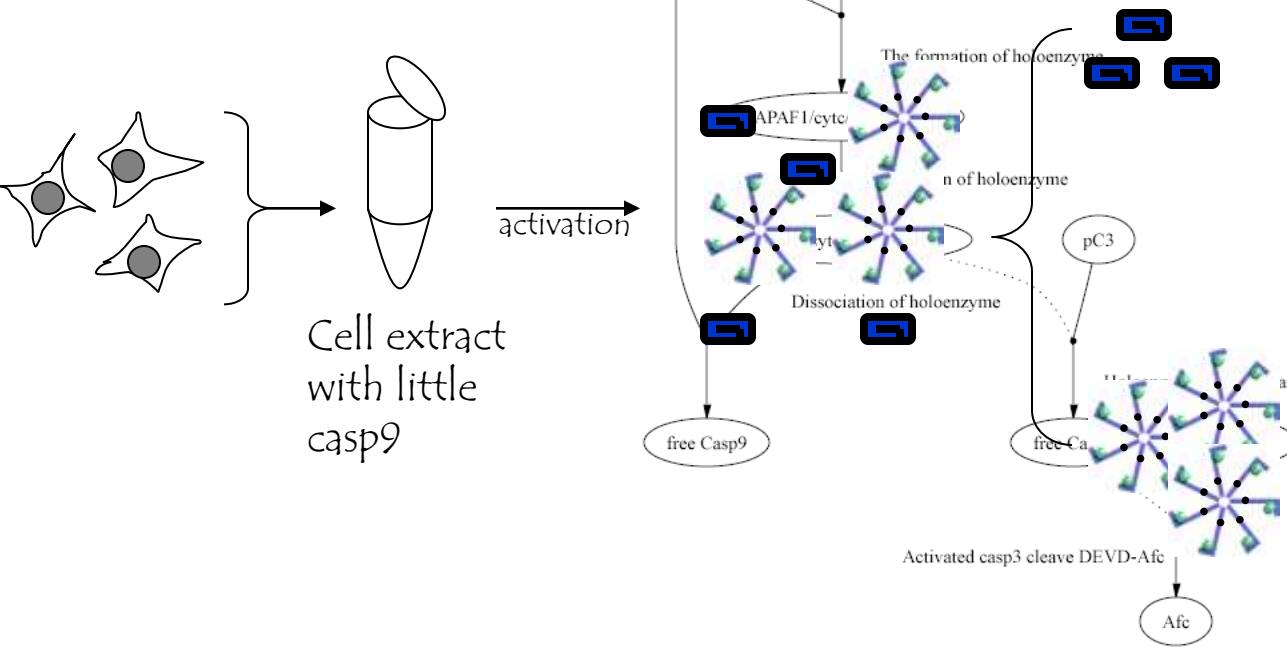
Reversibility?





- Recombinant system:
  - cytochrome c, caspase-9, APAF1
- Purification of endogenous APAF1/cytc oligomer



Cell extract with little casp9

Adding back

Cell extract with little APAF

[APAF1/cytc/dATP] ⟶ caspase3 activity

Linear dependence?

XS-Systems:
(AAMC M. et al. 2001-2009)

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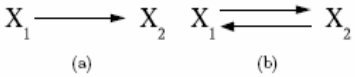

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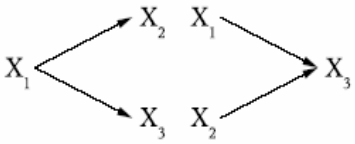

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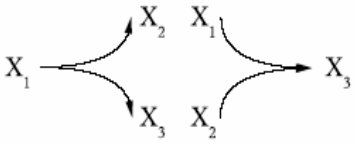

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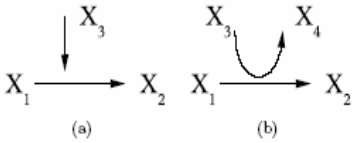

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Formal Definition of S-system

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

- $DV = \{X_1, \ldots, X_n\}$ *is a finite non empty set of* dependent variables *ranging over the domains* $D_1, \ldots, D_n$, *respectively;*
- $IV = \{X_{n+1}, \ldots, X_{n+m}\}$ *is a finite set of* independent variables *ranging over the domains* $D_{n+1}, \ldots, D_{n+m}$, *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*

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

  with γ_j *called* rate constraints.

Verifying temporal properties of a reactive system

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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

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

Subway Map of Cancer

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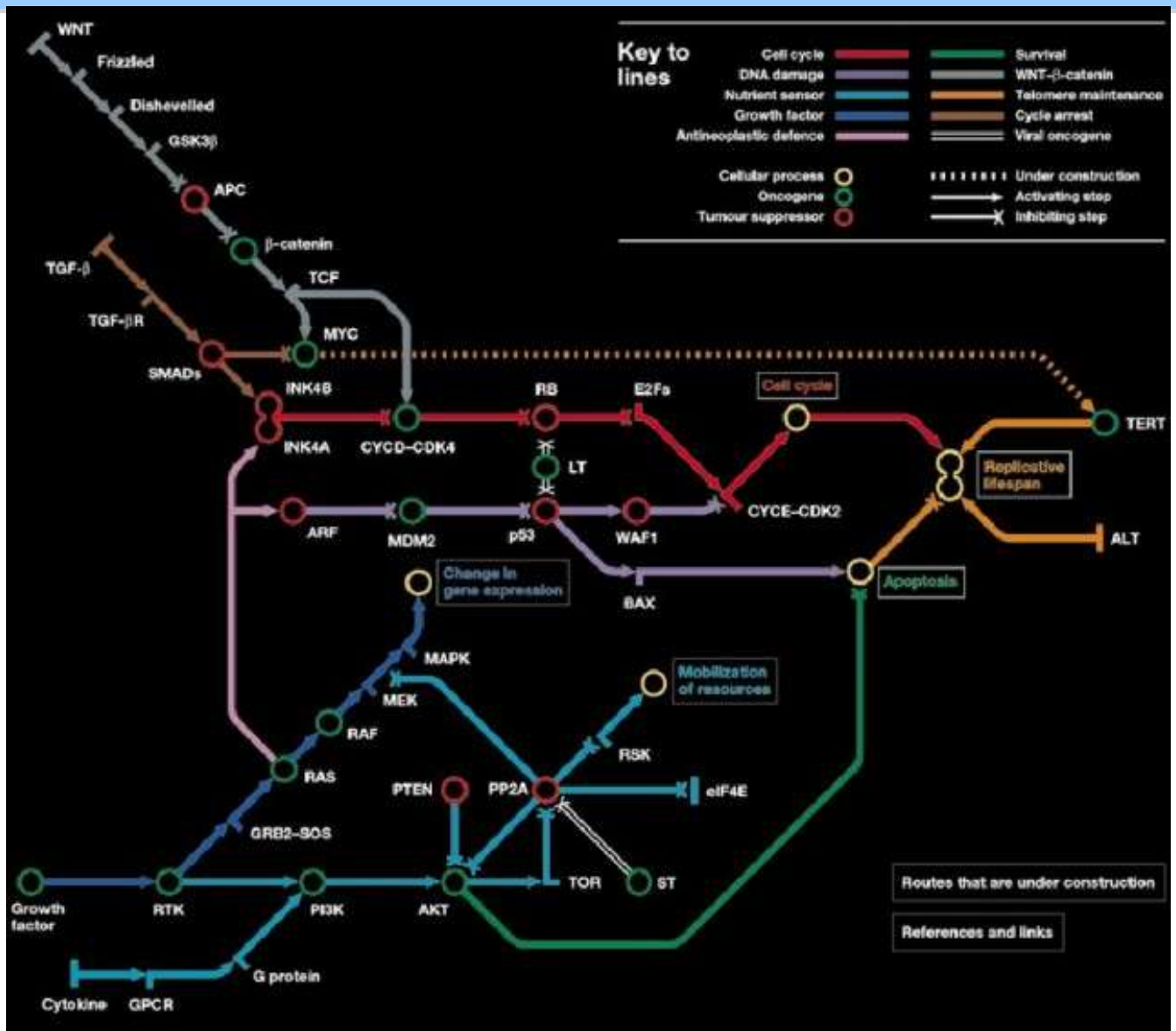

Is this View of Cancer Necessarily Accurate ?

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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

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

The New Synthesis

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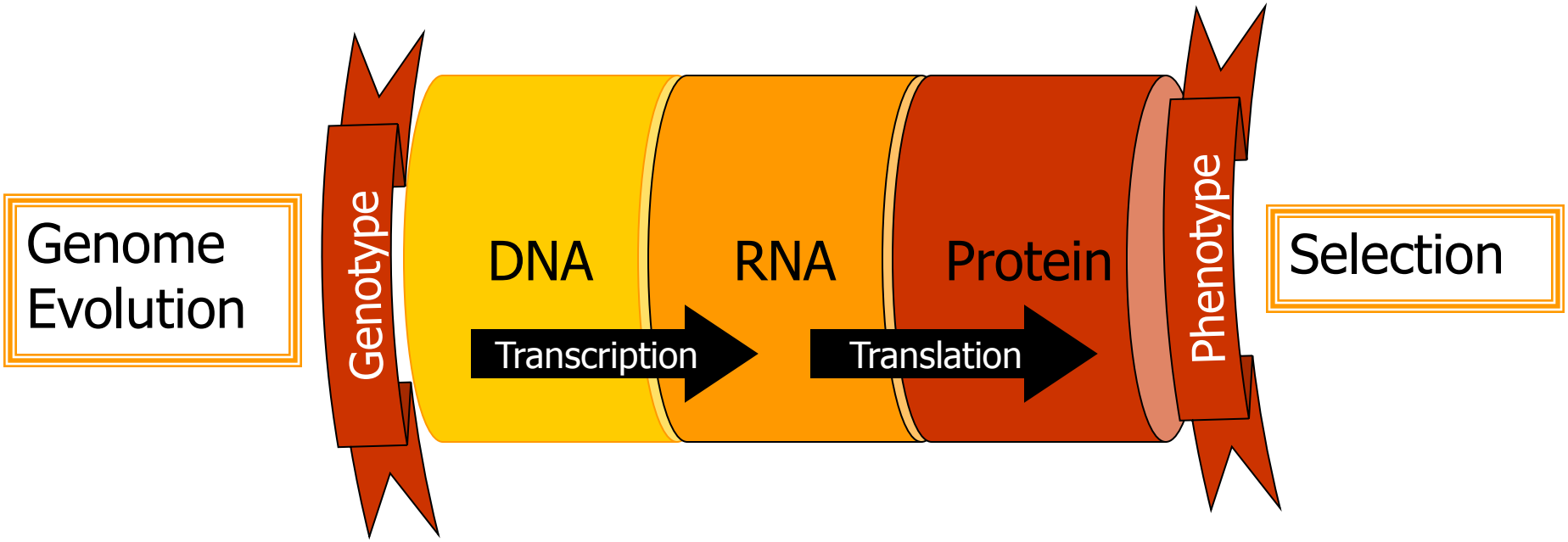

Cancer Initiation and Progression

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Mutations, Translocations, Amplifications, Deletions

Epigenomics (Hyper & Hypo-Methylation)

Alternate Splicing

Cancer Initiation and Progression

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

Amplifications & Deletions

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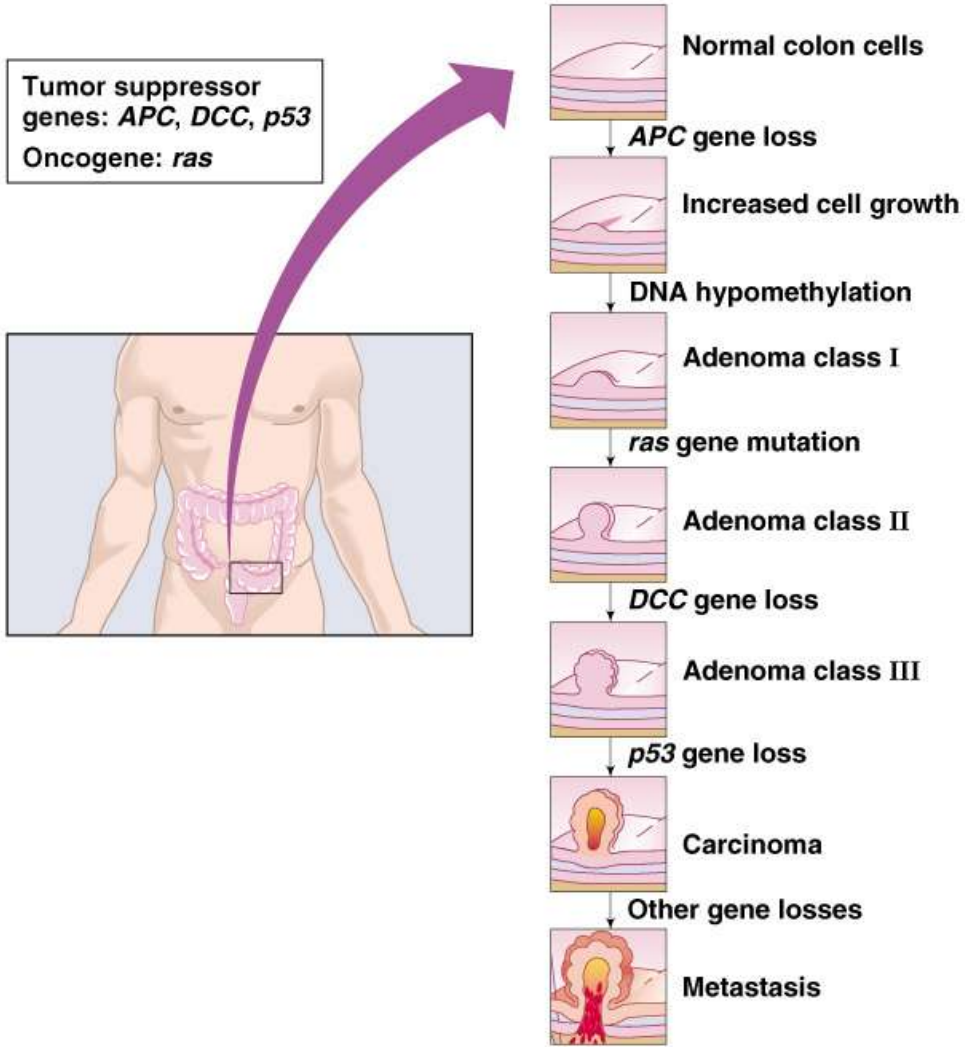

Mutation in a TSG

Epigenomics

Conversion of a Proto-Oncogene

Deletion of a TSG

Deletion of a TSG

Karyotyping

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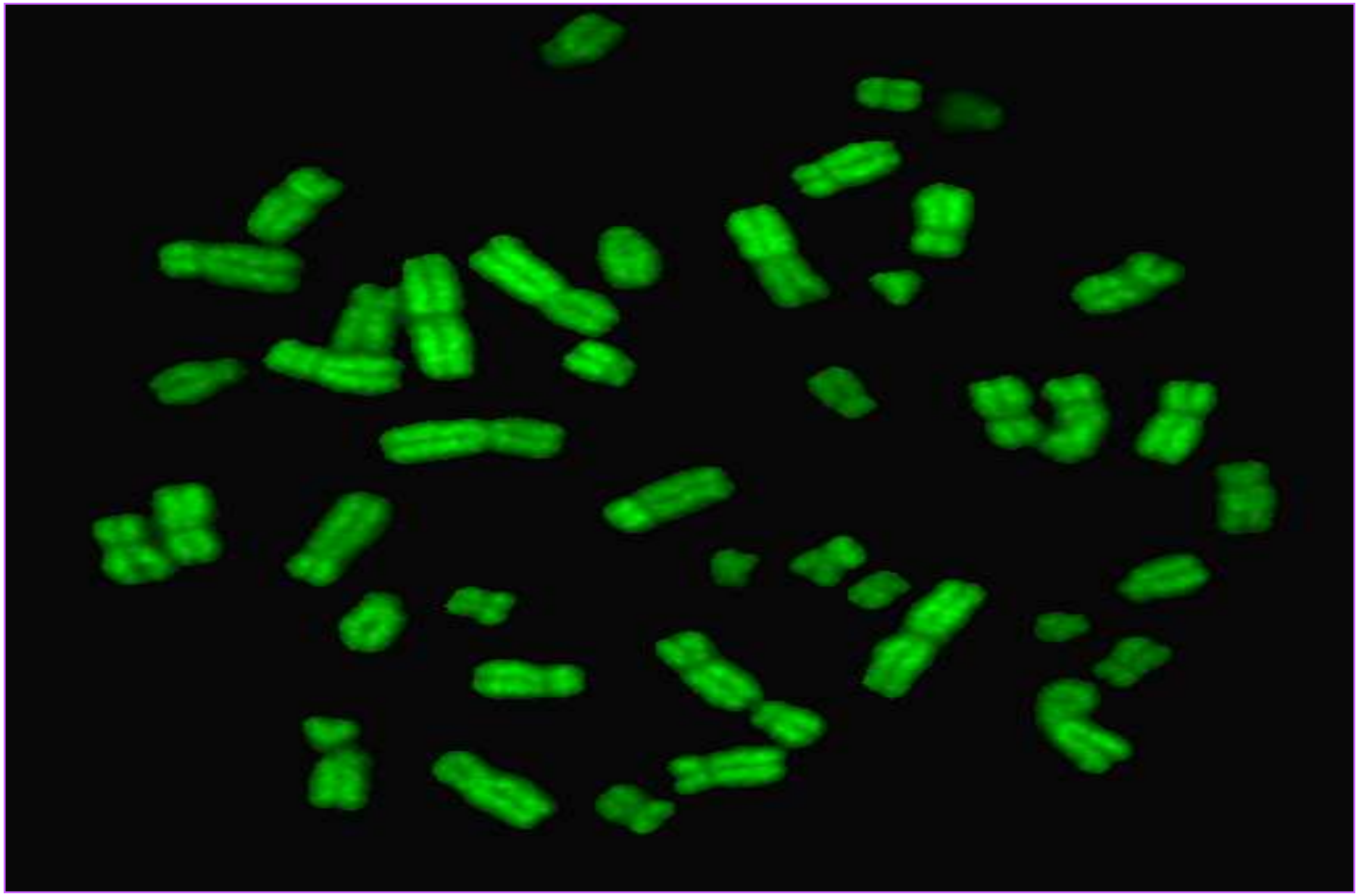

Microarray Analysis of Cancer Genome

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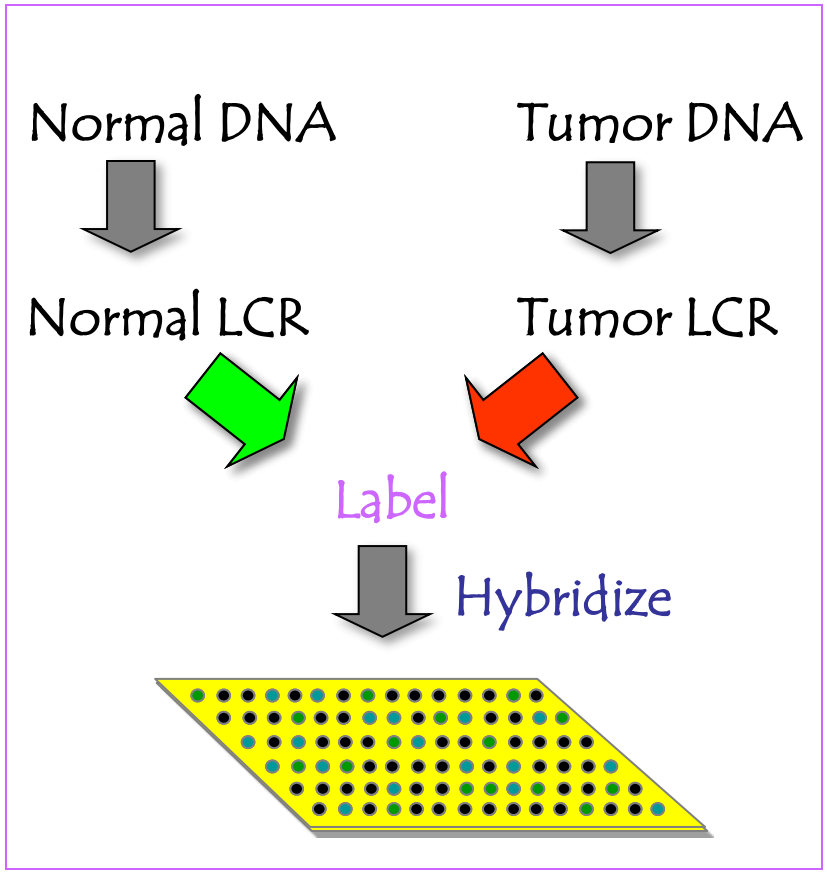

- Representations are reproducible samplings of DNA populations in which the resulting DNA has a reduced complexity.
  - Array probes derived from low complexity representations of the normal genome
  - We measure differences in gene copy number between normal and tumor samples ratiometrically

Daruwala et al. (PNAS, 2004)

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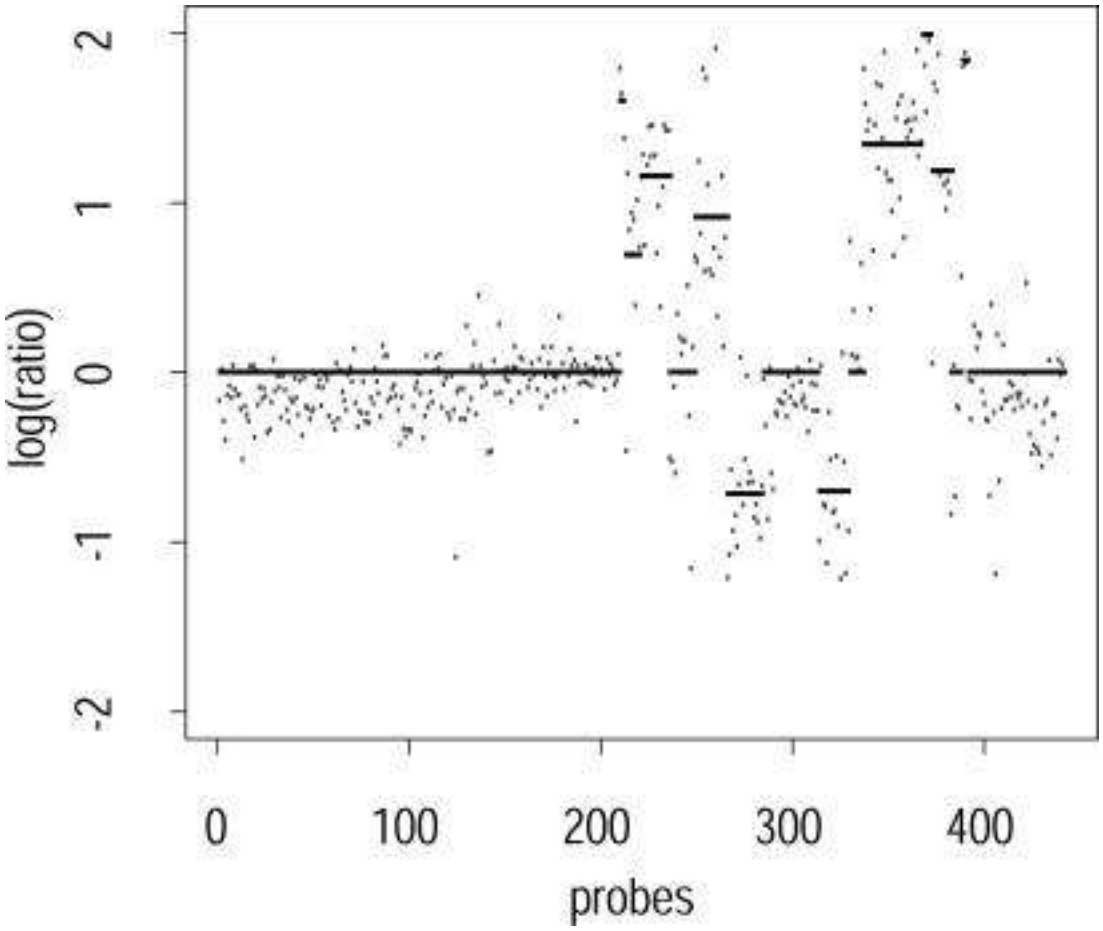

Allelic Frequencies: Cancer & Normal
(Anantharaman et al. unpublished)

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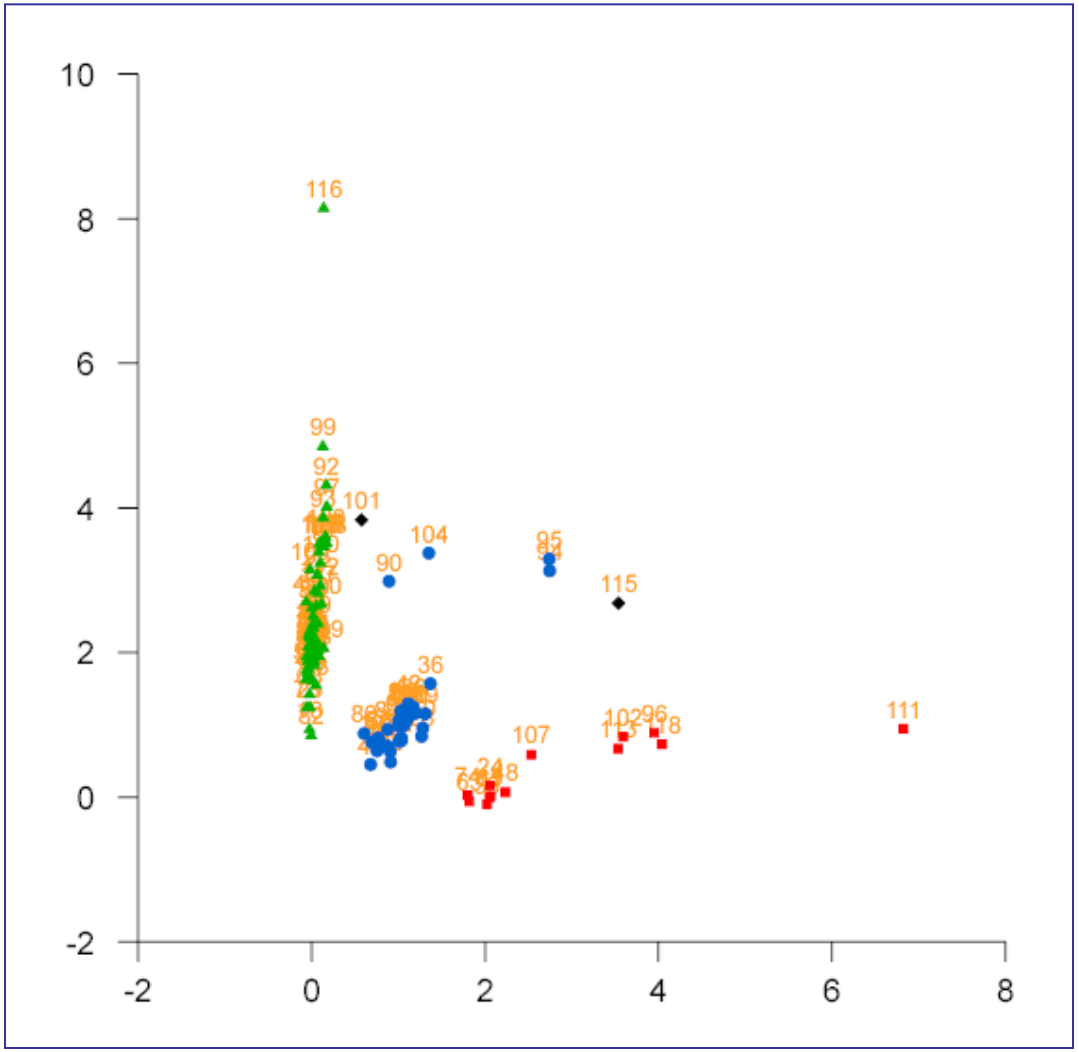

Cell Stress: Glycosylation

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- 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 (gylycosylation) 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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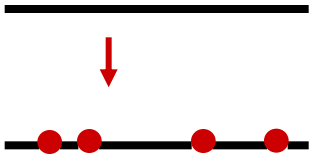
PolyA cDNAs in solution

Shear Flow

cDNAs fixed to surface



Restriction Enzyme ex. '*Rsa I*'

cDNAs 'coded'
ex. '*GTAC*'

0010100000100010

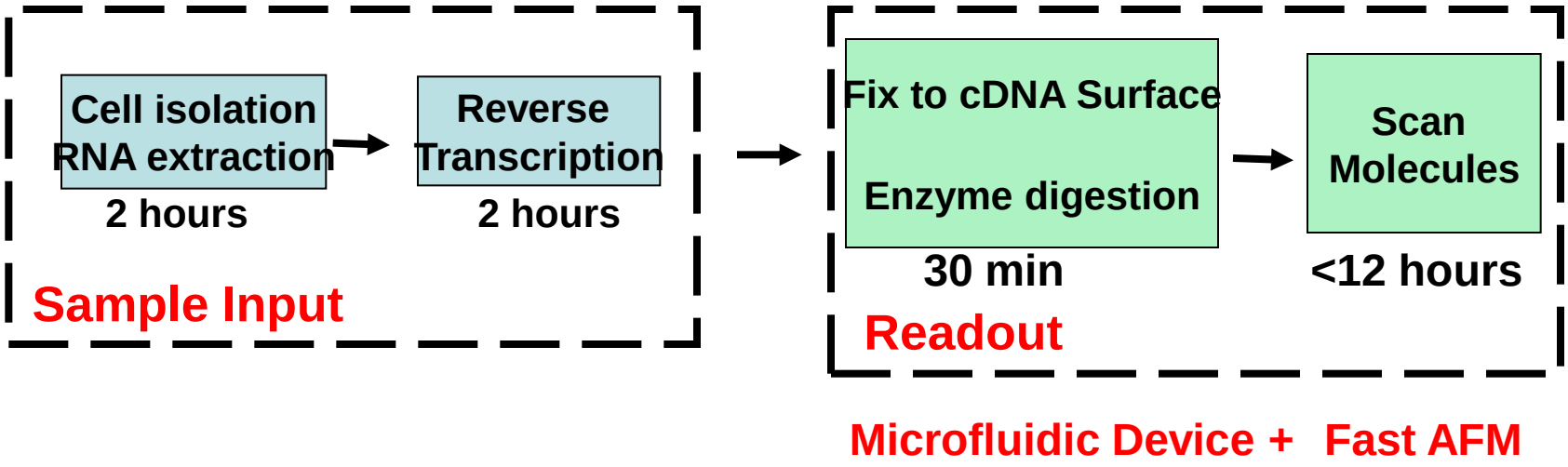
AFM Imaging

Image Processing, Pattern Matching

Reed, et al., Nanotechnology, 2007

Single Molecule Restriction Map

MCAI 2.0



AFM vs Sequence

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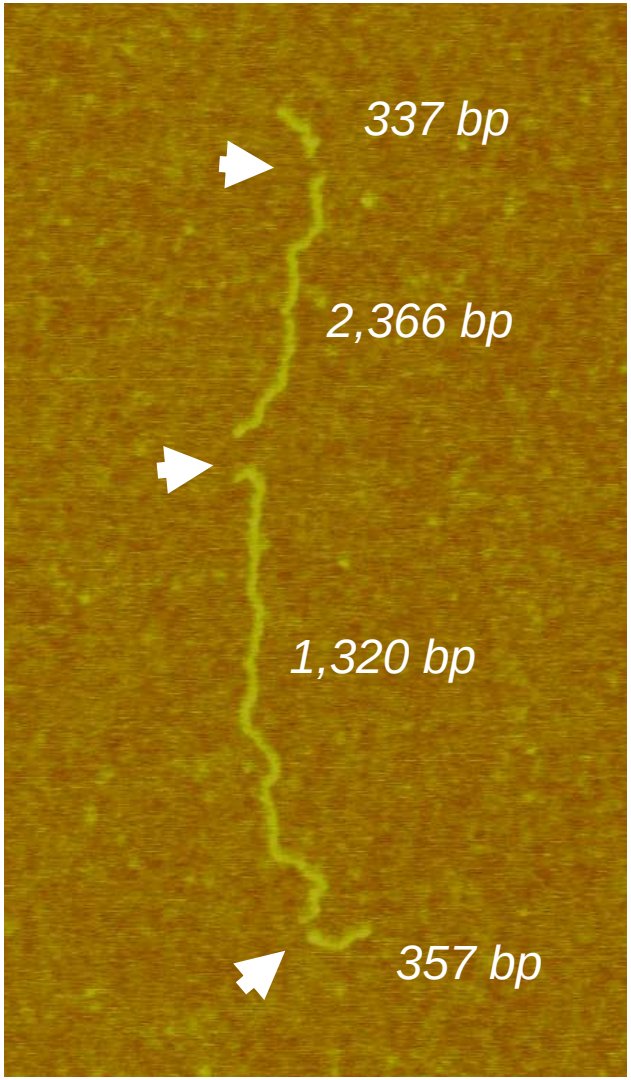
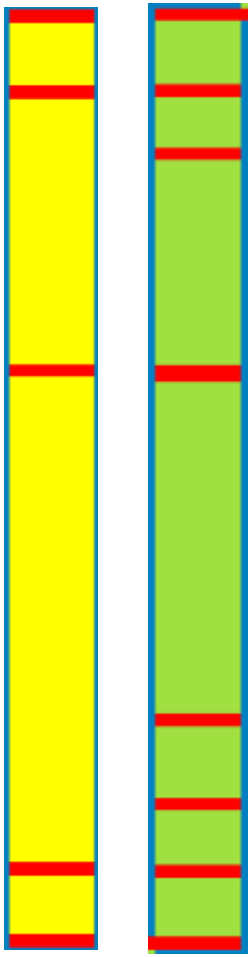


870 x 1,500 nm



AFM **Seq.**

Identify and Count

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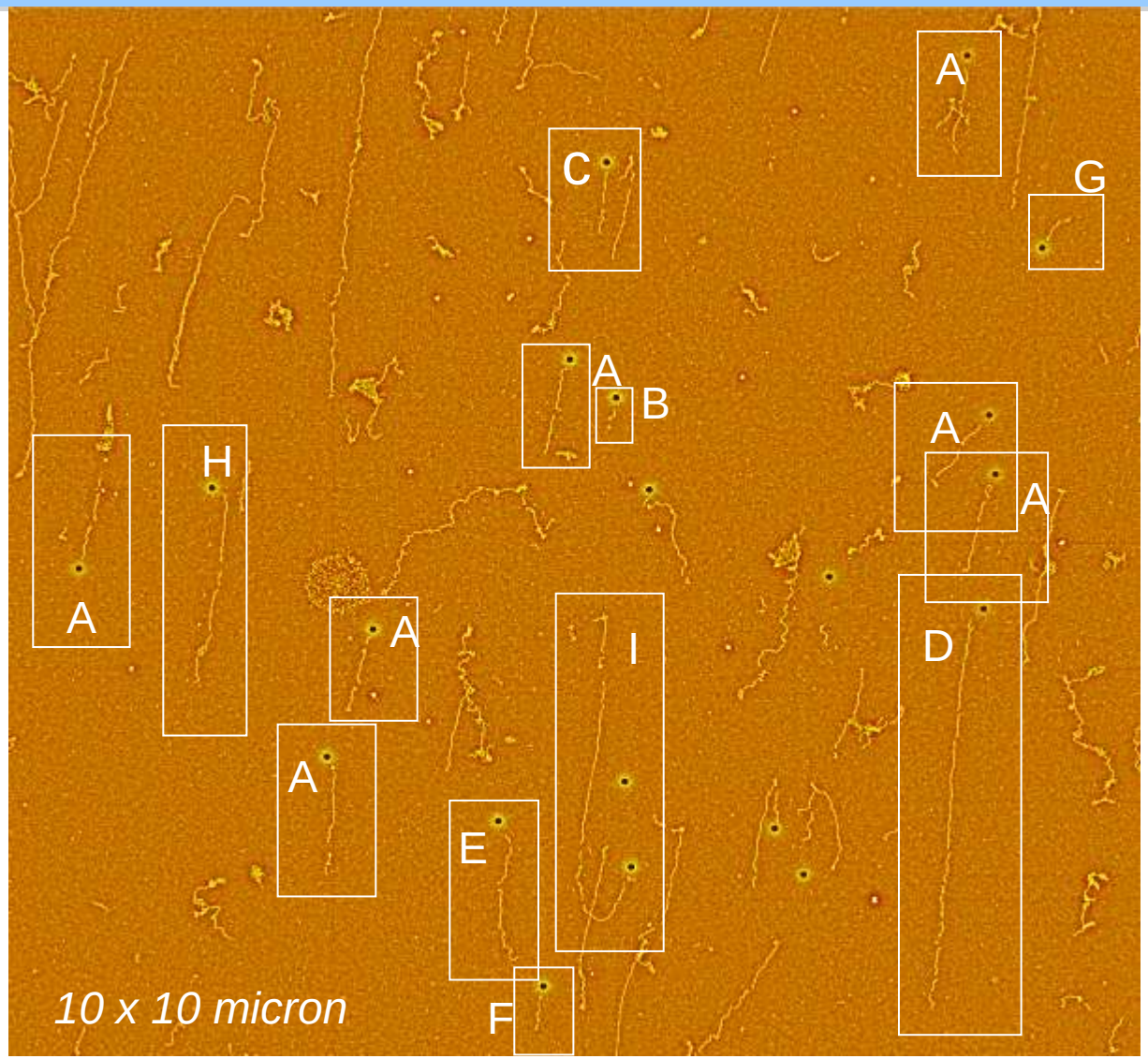
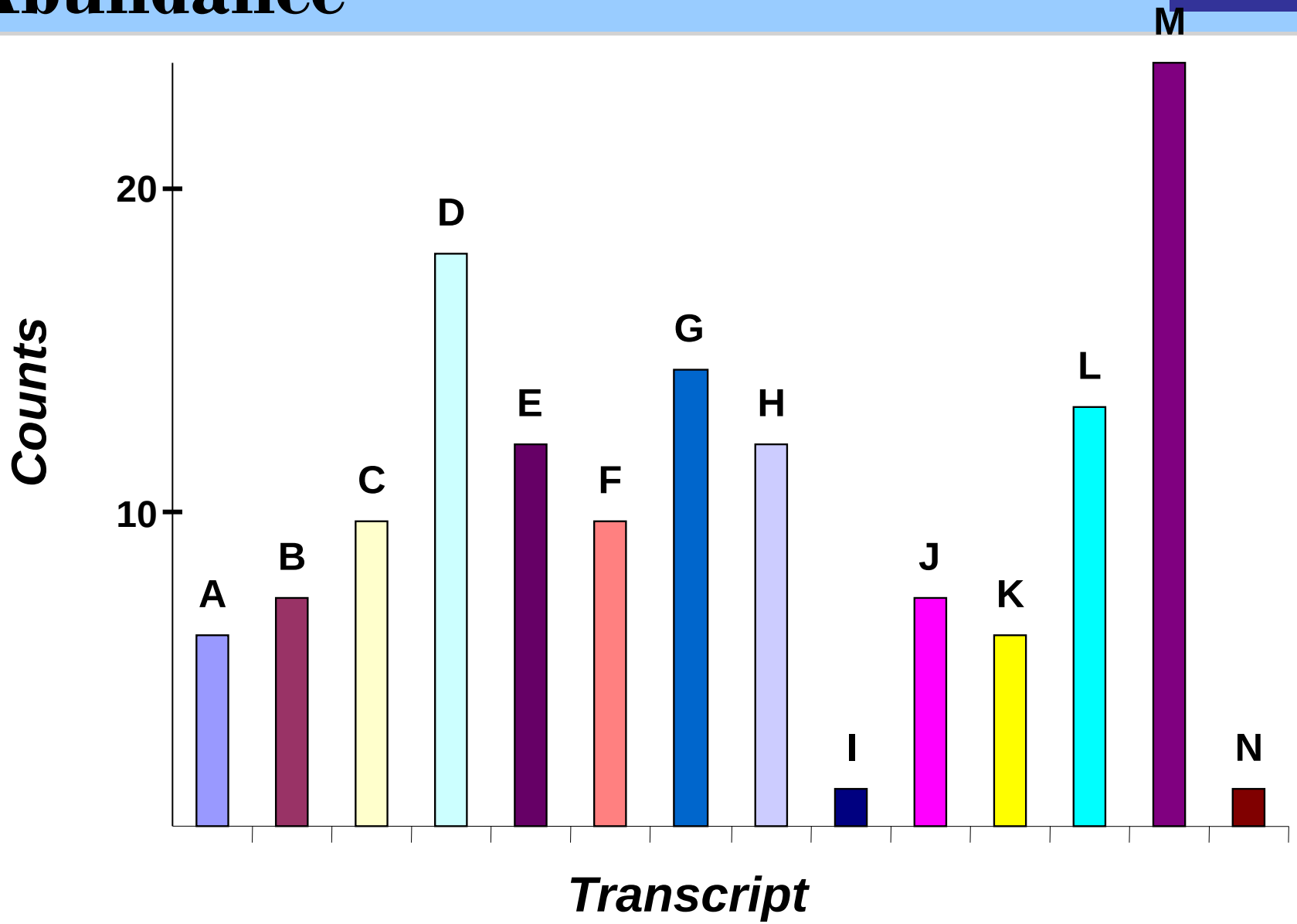


Histogram of Transcript Abundance

MCAI 2.0



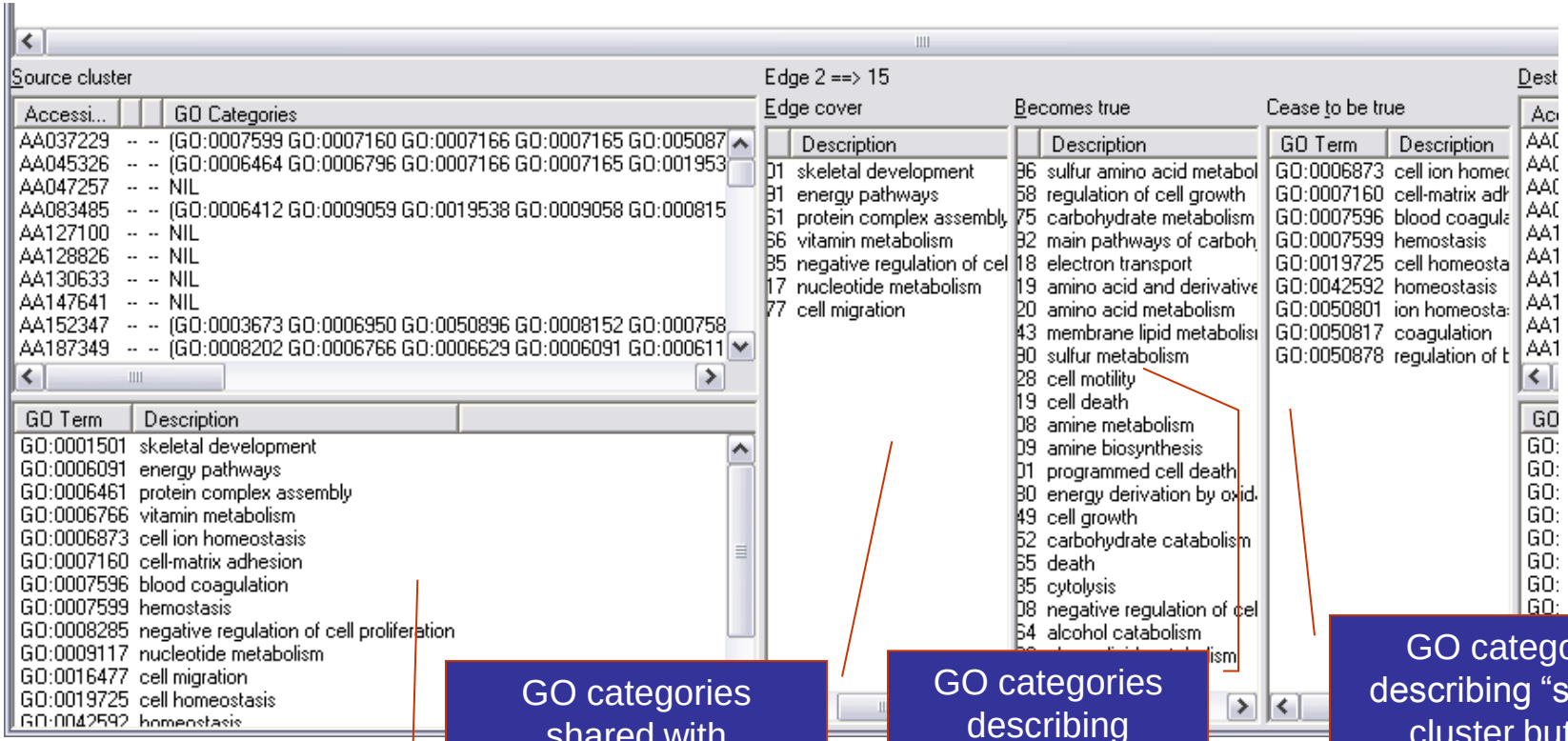
Models that are Concepty

MCAI 2.0

- **“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

MCAI 2.0



GO categories describing genes in "source" cluster

GO categories shared with "destination" cluster

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

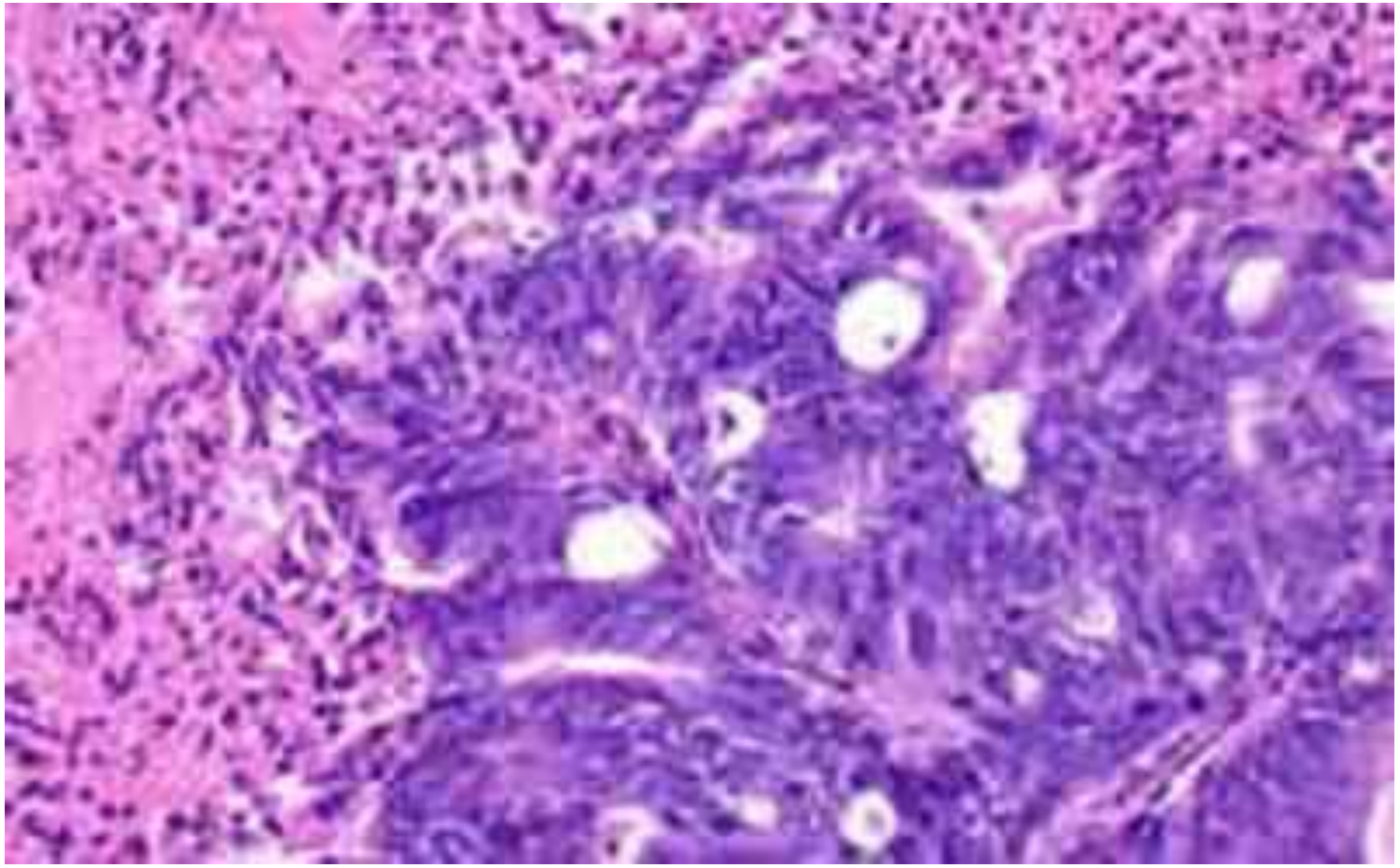
GO categories describing "source" cluster but not "destination"

Unknown Unknown Biology

MCAI 2.0

Pathologist's View

MCAI 2.0



Healthy and diseased pancreas cells

A Challenge

MCAI 2.0

- **“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

MCAI 2.0

- **“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.*

Foci

MCAI 2.0

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

Translational Systems Biology

MCAI 2.0

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- "Metamorphosis: The Coming Transformation of Translational Systems Biology," (with S. Kleinberg), *ACM Queue* 2009.

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MCAI 2.0

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MCAI 2.0

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- "Model Building and Model Checking for Biochemical Processes," (with M. Antoniotti, A. Policriti and N. Ugel), *Cell Biochemistry and Biophysics* (CBB), 38(3): 271-286, Humana Press, June, 2003.
- "Taming the Complexity of Biochemical Models through Bisimulation and Collapsing: Theory and Practice," (with M. Antoniotti, C.Piazza, A. Policriti and M. Simeoni), *Theoretical Computer Science*, 325(1): 45-67, 2004.
- "Simpathica: A Computational Systems Biology Tool within the Valis Bioinformatics Environment," (with M. Antoniotti, S. Paxia and N. Ugel), *Computational Systems Biology*, (Ed. E. Eiles and A. Kriete), Elsevier, 2005.
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MCAI 2.0

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Optical Mapping

MCAI 2.0

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- “Genomics via Optical Mapping II: Ordered Restriction Maps,” (with T.S. Anantharaman and D.C. Schwartz), *Journal of Computational Biology*, 4(2):91-118, 1997.
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- “Optical Mapping,” *Encyclopedia of the Human Genome*, 4: 448-453, Nature Publishing Group, Macmillan Publishers Limited, London, UK, June, 2003.

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MCAI 2.0

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MCAI 2.0

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Ontology: GOALIE

MCAI 2.0

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- "Systems Biology via Redescription and Ontologies (III): Protein Classification using Malaria Parasite's Temporal Transcriptomic Profiles," (with A. Mitrofanova et al.), *2008 IEEE International Conference on Bioinformatics and Biomedicine*, BIBM'08, 2008.
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Answer to Cancer

MCAI 2.0

- **“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