Death Team Presents: A SCREEN PLAY *A Mathematical Model of Apoptosis*

Death Team

MBI 2007 Project Leaders:
Baltazar Aguda and Chiu-Yen Kao

August 10, 2007

Outline

Introduction-Trailers

Background: The directors and actors

Directors (Project Leaders)

- Baltazar Aguda
- Chiu-Yen Kao

Introduction-Trailers

Background: The directors and actors

Directors (Project Leaders)

- Baltazar Aguda
- Chiu-Yen Kao

Actors in order of appearance (Death Team)

- Heather Harrington Imperial College London
- Samik Ghosh University of Texas at Arlington
- Kenneth Ho California Institute of Technology
- K.C. Tung UT Southwestern Medical Center

Introduction-Trailers

Background: The directors and actors

Introduction-Trailers

Background: What is apoptosis?

- The development and maintenance of homeostasis in multi-cellular organisms arises from a complex interplay of cellular processes.

Introduction-Trailers

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What is Apoptosis?

Apoptosis, or programmed cell death is one of the key physiological mechanisms employed by the cell.

Introduction-Trailers

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Apoptosis, or programmed cell death is one of the key physiological mechanisms employed by the cell.

- What distinguishes apoptosis from other types of cell death?

Introduction-Trailers

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What is Apoptosis?

Apoptosis, or programmed cell death is one of the key physiological mechanisms employed by the cell.

- What distinguishes apoptosis from other types of cell death?

A hallmark of the apoptotic process is its "programmed" nature

i.e. it is characterized by a controlled sequence of well-defined steps which results in cell destruction.

Introduction

Background: Implications of apoptosis

- In the adult human body, several thousands of cells are regulated by mitosis and apoptosis continuously.
  - Formation of independent digits by massive cell death
  - Adult brain formation
  - Reproductive organ development

Introduction

Motivation to model apoptosis: Inappropriate cell decisions

- Inappropriate apoptosis may result in many physiological health problems.

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Insufficient apoptosis

In cancer cells, insufficient apoptosis leads to cell accumulation!

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- There are two possible outcomes:

Insufficient apoptosis

In cancer cells, insufficient apoptosis leads to cell accumulation!

Excessive cell death

Various neurodegerative diseases (Parkinson's or Alzheimer's disease) are associated with excessive apoptosis.

Introduction

Motivation to model apoptosis: Significance

- Apoptosis also plays a significant part in immune system response.
- The apoptotic pathway is characterized by complex interactions.
- Scientists do not fully understand the entire pathway, key characteristics have been identified.

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Motivation to model apoptosis: Significance

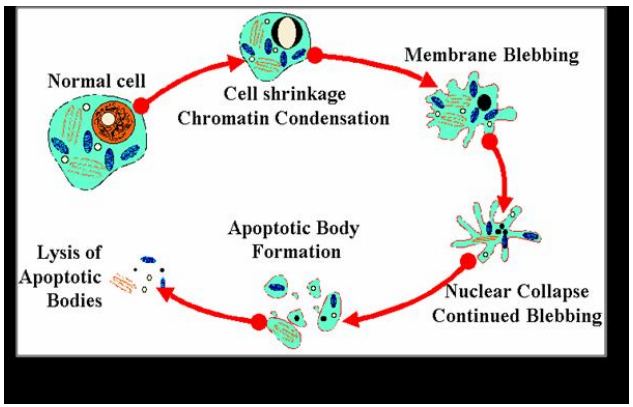
- Apoptosis also plays a significant part in immune system response.
- The apoptotic pathway is characterized by complex interactions.
- Scientists do not fully understand the entire pathway, key characteristics have been identified.
- We model to gain insight into the biological mechanisms at the cellular level

Introduction

The Biology of Apoptosis: Caspases and signaling pathways

Why is death clean?

Death is clean due to proteases that degrade specific proteins during apoptosis.



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The Biology of Apoptosis: Caspases and signaling pathways

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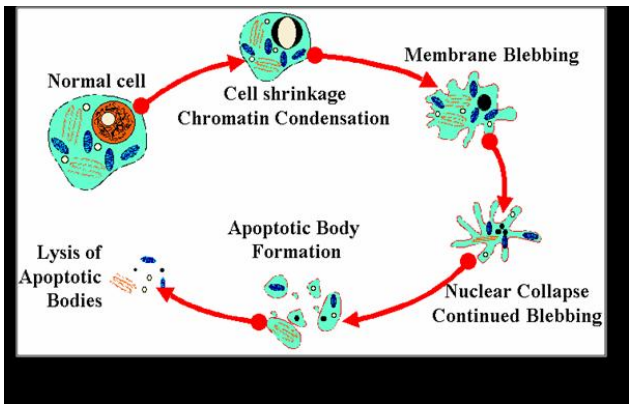
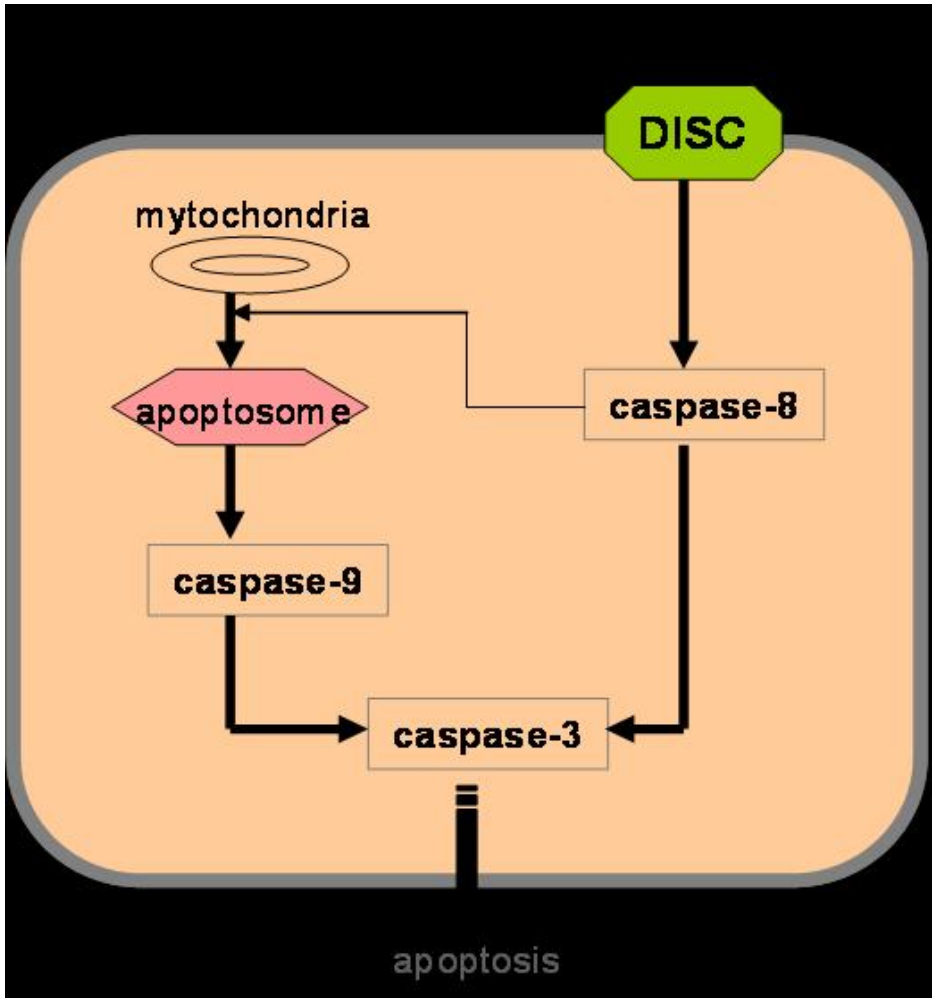
What are Caspases?

Caspases (cysteine-containing aspartate-specific proteases) are enzymes involved in apoptosis. There are initiators and effector caspases.



Introduction

The Biology of Apoptosis: Schematic figure



Introduction

The Biology of Apoptosis: Signaling pathways

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  1. Extrinsic (membrane receptor-mediated pathway)
     - Ligands bind to receptors to form DISC/FADD (death-inducing signaling complex).
     - DISC $\longrightarrow$ caspase 8 $\longrightarrow$ caspase 3 $\longrightarrow$ cell death.

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  2. Intrinsic (mitochondria-mediated pathway)
     - BID or other stress cause mitochondria to release cytochrome c.
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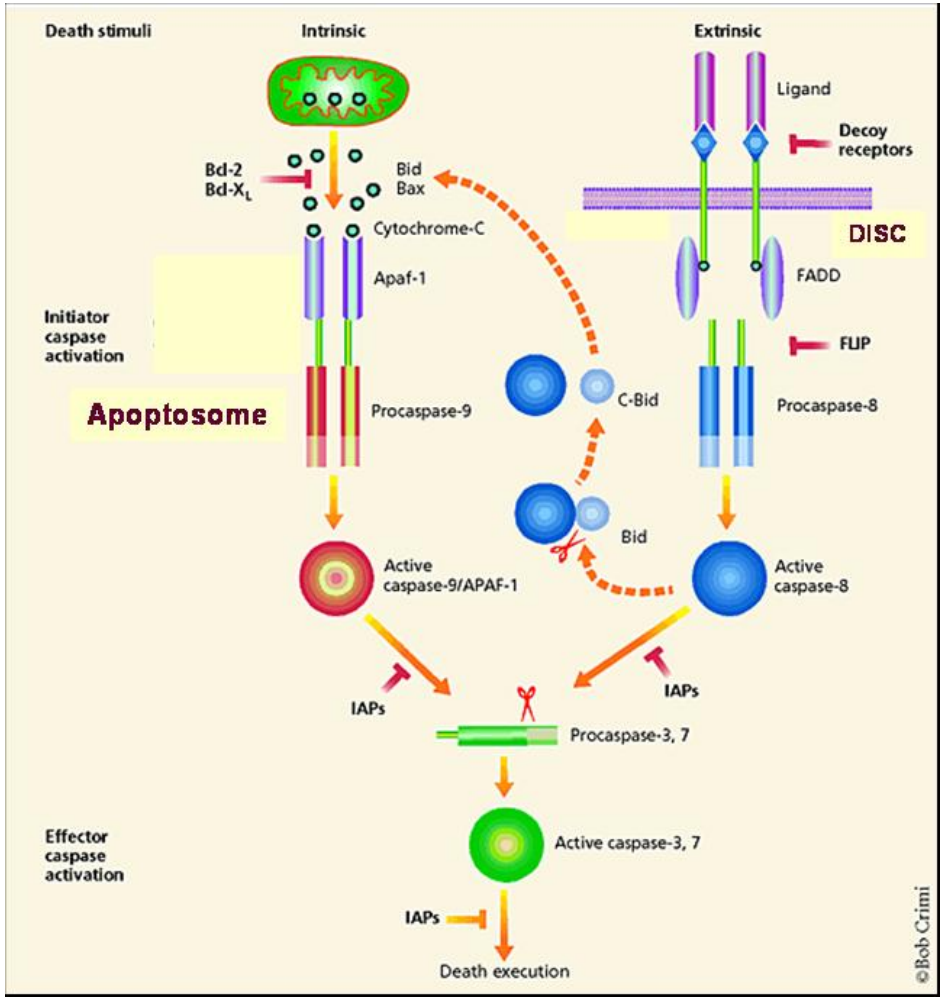
     - Apoptosome $\longrightarrow$ caspase 9 $\longrightarrow$ caspase 3 $\longrightarrow$ cell death.
- Additionally, there is inhibition, cross-talk and feedback mechanisms between the two pathways.

Introduction

The Biology of Apoptosis: Schematic figure



Zheng 2000, *Nat Biotechnology*

Introduction

Existing Models: Overview

Types of Models

- Extrinsic

Introduction

Existing Models: Overview

Types of Models

- Extrinsic
- Intrinsic

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Existing Models: Overview

Types of Models

- Extrinsic
- Intrinsic
- Integrated

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Existing Models: Overview

Types of Models

- Extrinsic
- Intrinsic
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- Note: While many mathematical models describing particular components of the apoptotic pathway exist, these models may be inelegant, limited in scope of a pathway (ie only considering one pathway or activation) or have a complex structure requiring knowledge of numerous biological parameters (which are often estimated).

Introduction

Existing Models: Extrinsic

Eissing

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Bistability Analyses of a Caspase Activation Model for Receptor-induced Apoptosis*

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Introduction

Existing Models: Extrinsic

Eissing

$$C8^* + C3 \rightarrow C8^* + C3^*$$

Reaction 1

$$C8 + C3^* \rightarrow C8^* + C3^*$$

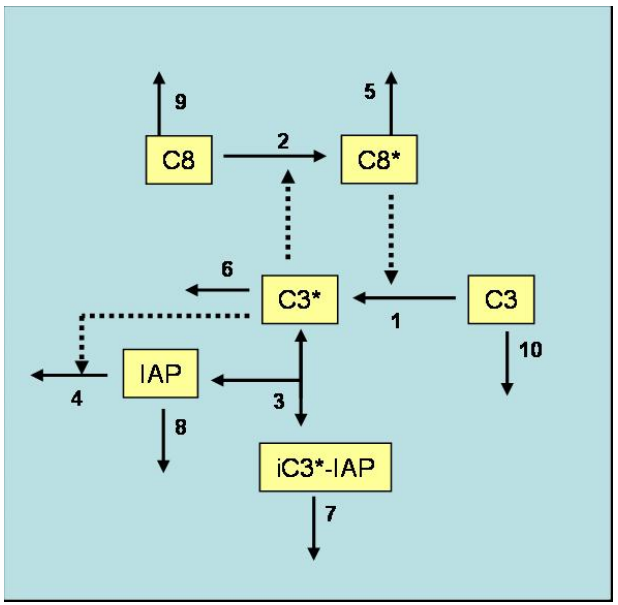
Reaction 2

$$C3^* + IAP \leftrightarrow iC3^* \sim IAP$$

Reaction 3

$$C3^* + IAP \rightarrow C3^*$$

Reaction 4



Introduction

Existing Models: Extrinsic

Eissing

- Develop their model based on mass action kinetics.

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- *Criticism:* Do not consider the dynamics of the activating stimulus.
- *Criticism:* This bistability claim is based on parameter adjustments, but is not shown analytically.

Introduction

Existing Models: Extrinsic

Lai and Jackson

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Lai and Jackson

- Lai and Jackson formulate a mathematical model describing the process of DISC formation and activation.

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- Provides a comprehensive model of the receptor trimerization role necessary for apoptosis.

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Existing Models: Extrinsic

Lai and Jackson

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- Provides a comprehensive model of the receptor trimerization role necessary for apoptosis.
- *Criticism:* The model does not consider the downstream extrinsic pathway.

Introduction

Existing Models: Intrinsic

Nakabayashi and Sasaki

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- Nakabayashi and Sasaki explicitly model the formation of the apoptosome as a Apaf-1 heptamer.

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- Determine an optimal ratio of cytochrome C and inactive Apaf-1 for the rate of apoptosome formation.

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Existing Models: Intrinsic

Nakabayashi and Sasaki

- Nakabayashi and Sasaki explicitly model the formation of the apoptosome as a Apaf-1 heptamer.
- Determine an optimal ratio of cytochrome C and inactive Apaf-1 for the rate of apoptosome formation.
- *Criticism:* This model focuses only on the apoptosome formation without considering downstream activation of the caspase cascade.

Introduction

Existing Models: Intrinsic

Legewie *et al*

Introduction

Existing Models: Intrinsic

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- Represent the intrinsic pathway behavior through a system of biochemical equations (28 equations and 33 parameters).

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Existing Models: Intrinsic

Legewie *et al*

- Represent the intrinsic pathway behavior through a system of biochemical equations (28 equations and 33 parameters).
- Identifies inhibitors (IAPs) that mediates bistability and feedback mechanisms of caspase 3 and caspase 9.
- *Criticism:* The oligomerization of apoptosome (from Apaf-1 triggered by cytochrome C) is not considered.

Introduction

Existing Models: Integrated

Bagci *et al*

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- The authors study the role of Bax, Bid and Bcl-2 switching mechanisms as a regulator that ensures bistability in the mitochondria-mediated pathway.

Introduction

Existing Models: Integrated

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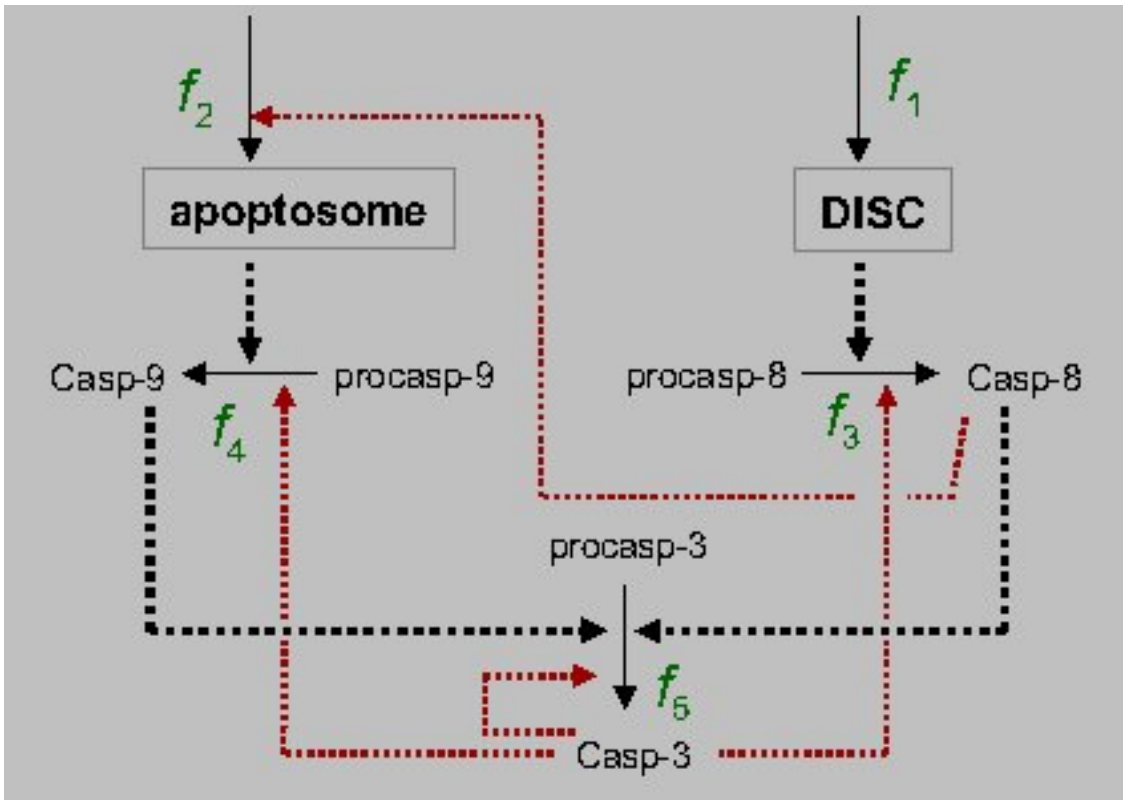
- The authors study the role of Bax, Bid and Bcl-2 switching mechanisms as a regulator that ensures bistability in the mitochondria-mediated pathway.
- *Criticism:* The mechanisms employed for activation of the intrinsic pathway does not capture known biological behavior.

Introduction

Novelties of our model: Modularized approach

Modularized Model



Introduction

Novelties of our model: What we did

Modularized Model

Integrated the dynamics of previous work as “modules.”

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- Caspase 8-3

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- Formation of DISC
- Formation of apoptosome
- Caspase 9-3

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Integrated the dynamics of previous work as "modules."

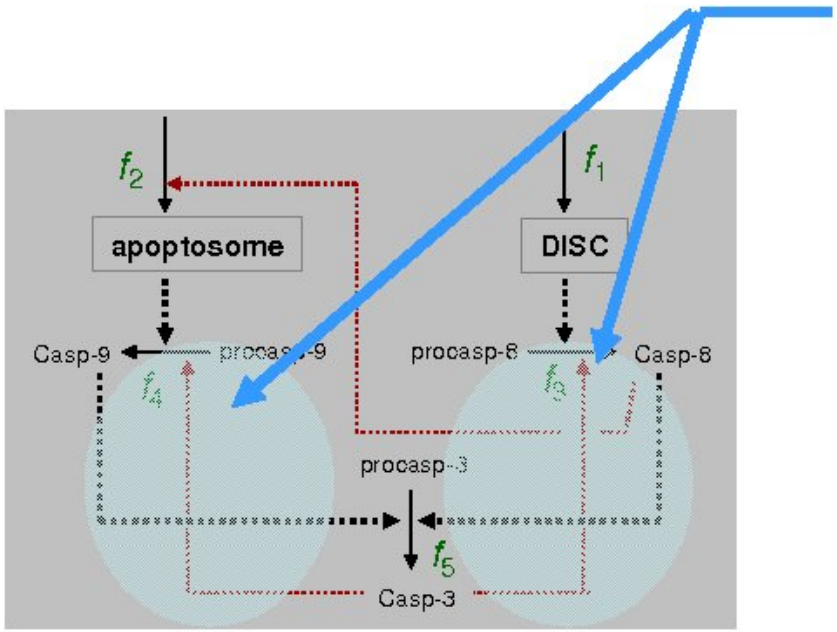
- Caspase 8-3
- Formation of DISC
- Formation of apoptosome
- Caspase 9-3
- Bid/Bax apoptotic switch
- Inhibitors of caspase (-8, -9, -3)

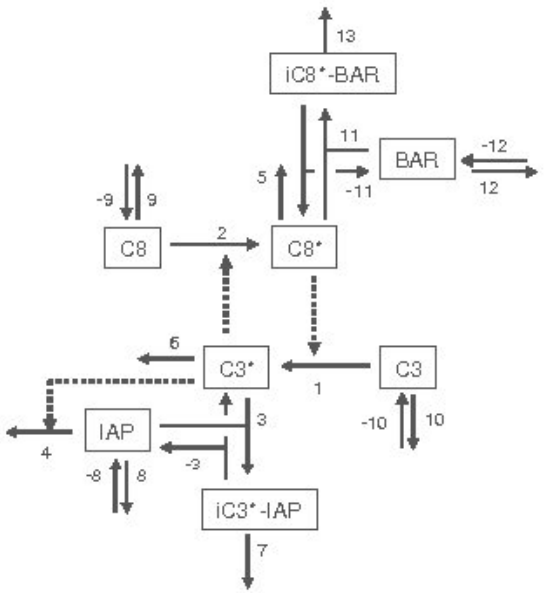
Introduction

Novelties of our model: What we did

Modularized Model

SCENE 2: SAMIK GHOSH





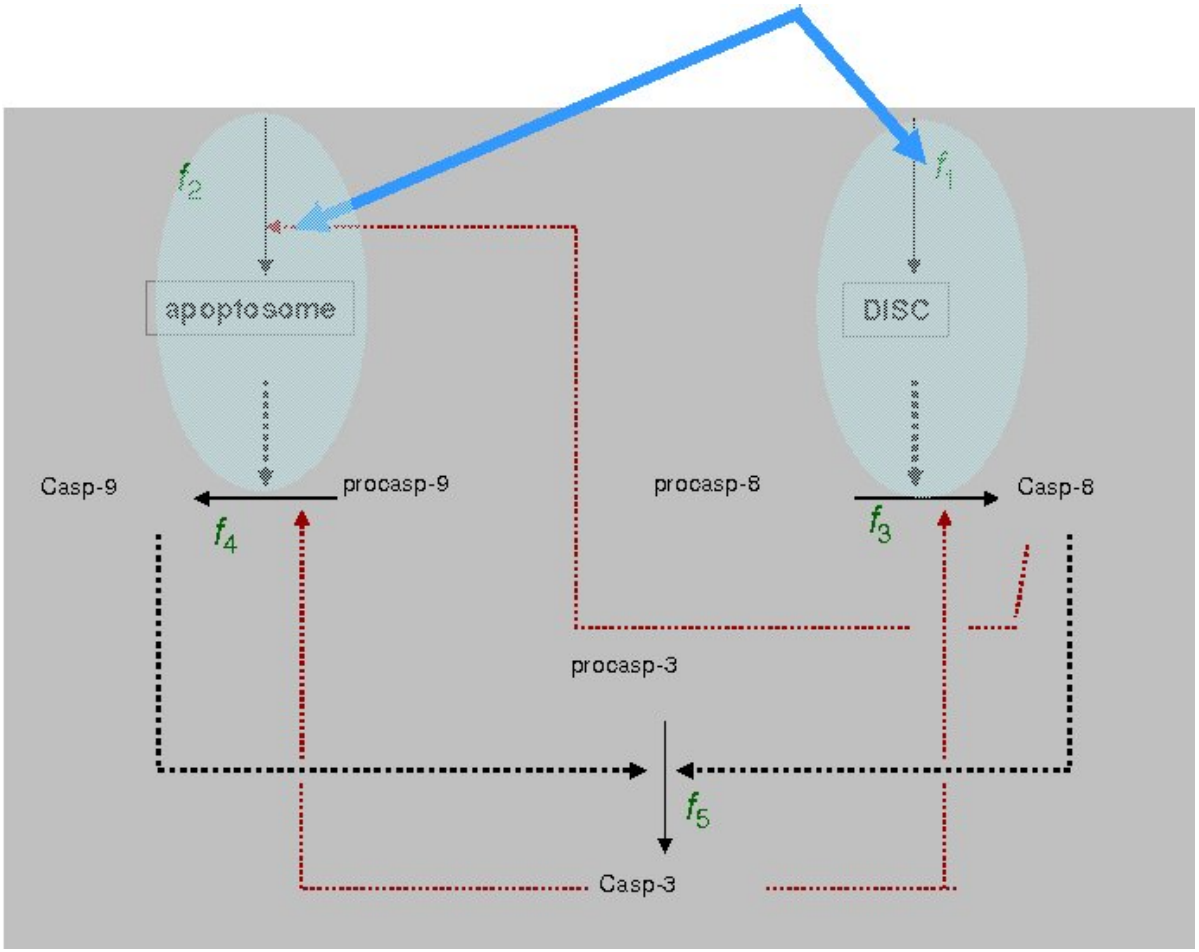
BISTABILITY IS ALSO PREDICTED. Figure from the Aguda & Friedman book.

Introduction

Novelties of our model: What we did

Modularized Model

SCENE 3: KEN HO

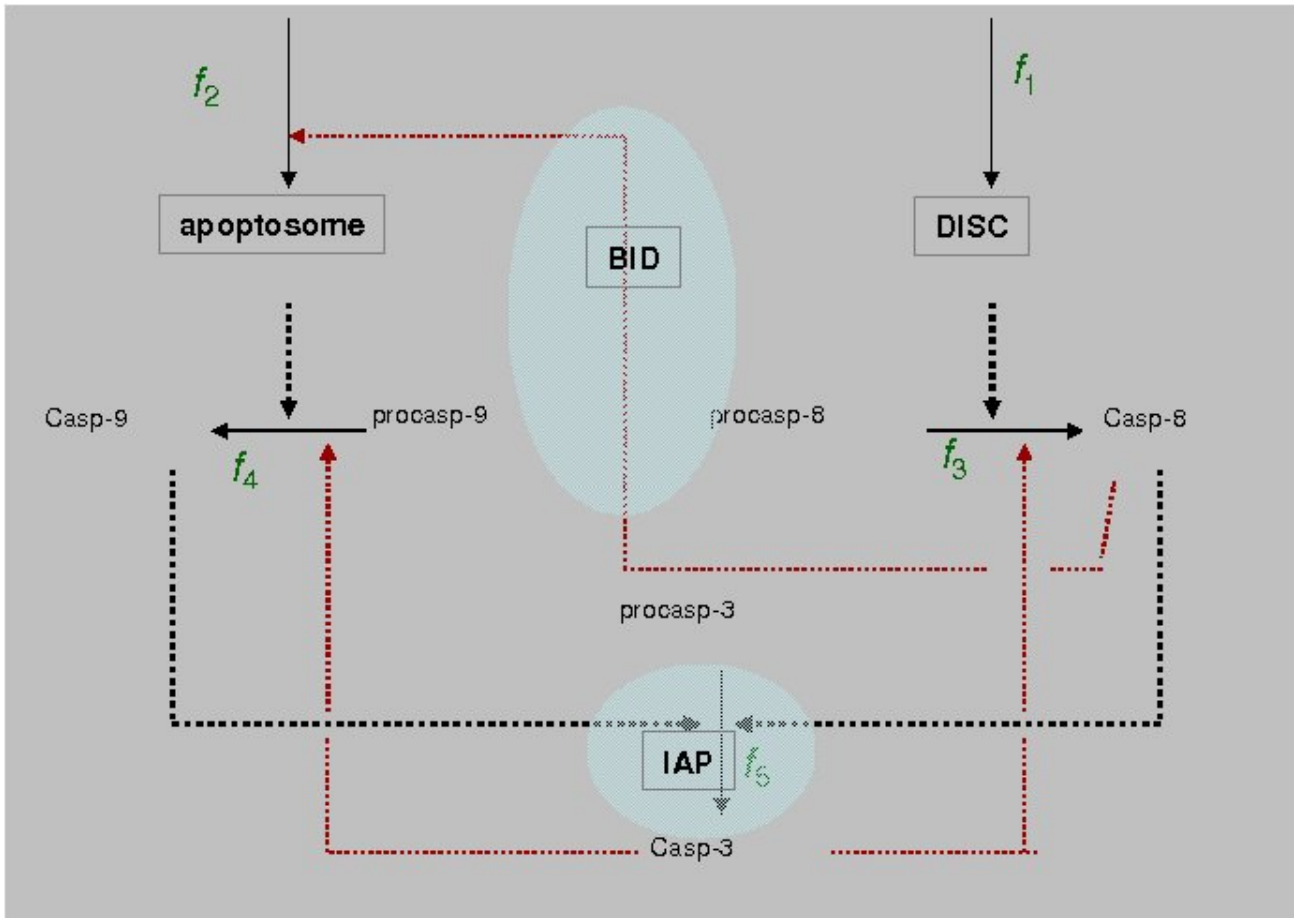


Introduction

Novelties of our model: What we did

Modularized Model

SCENE 4: KC TUNG



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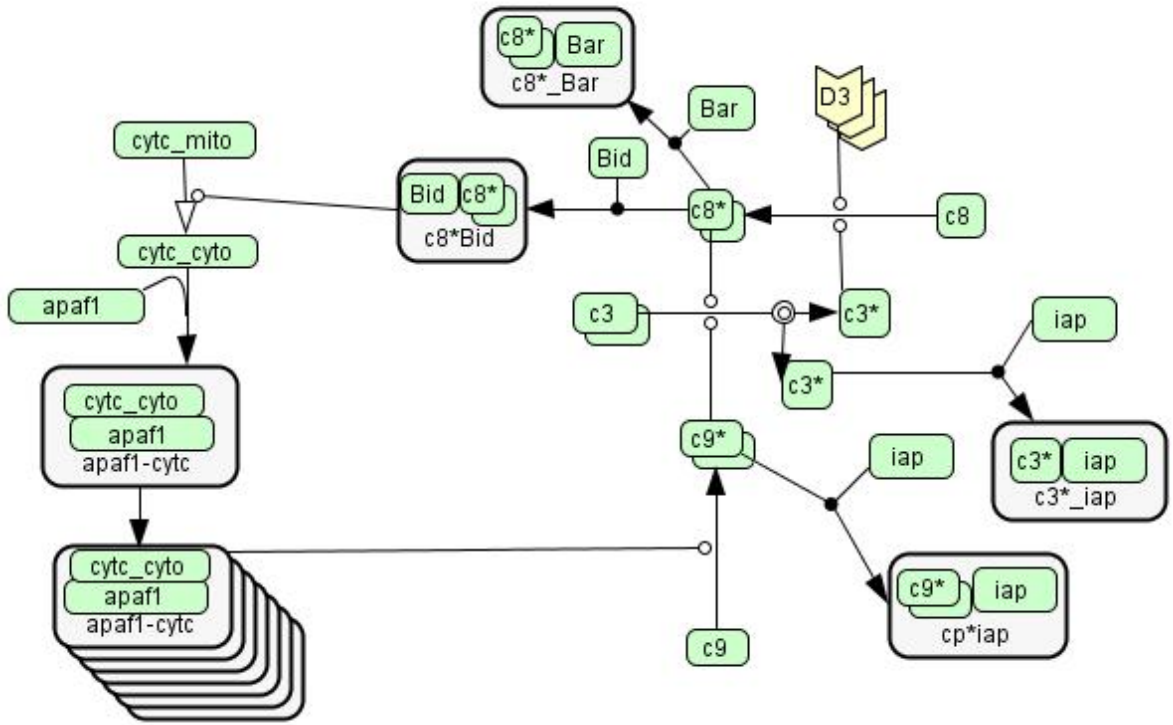

Introduction

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- Analysis of Caspase Modules

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- Mathematics of apoptosis activation

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Novelties of our model: What we did

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- Analysis of Caspase Modules
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- Integrated Model and Full System of ODEs

Introduction

Novelties of our model: What we did

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- Integrated Model and Full System of ODEs
- Simulations and Results

Introduction

Novelties of our model: Let the SCREEN PLAY begin

Like every good movie...

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Novelties of our model: Let the SCREEN PLAY begin

Like every good movie...

- We role played as individuals, all contributed equally.

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- We role played as individuals, all contributed equally.
- This work was done in very close collaboration.

Introduction

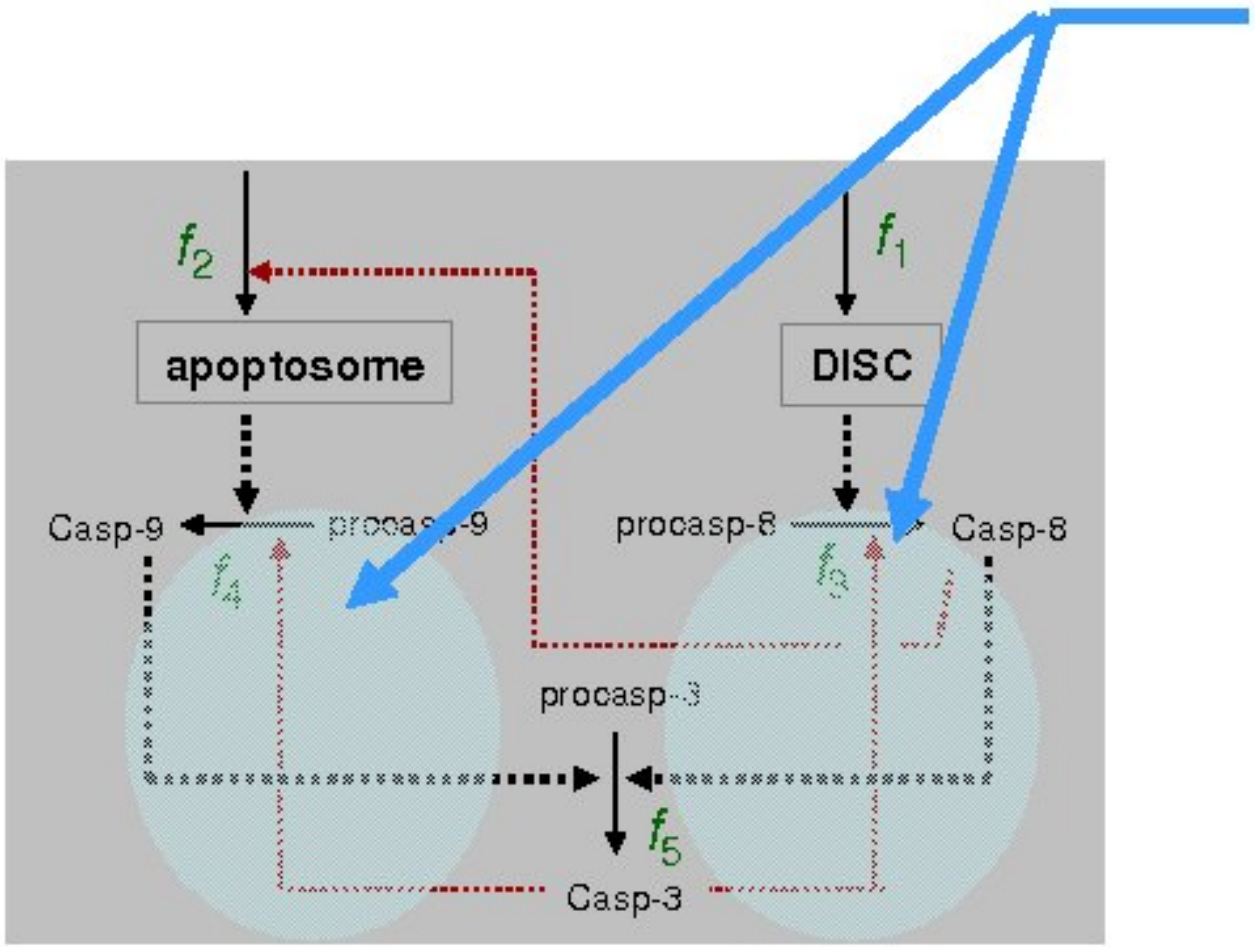
Novelties of our model: Let the SCREEN PLAY begin

Like every good movie...

- We role played as individuals, all contributed equally.
- This work was done in very close collaboration.
- Thank you for listening, please sit back and enjoy the rest of the show.

Analysis of caspase modules

Extrinsic and intrinsic modules



Analysis of caspase modules

Extrinsic C8/C3 module: Eissing model

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Reaction 1

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$$C3^* + IAP \leftrightarrow iC3^* \sim IAP$$

Reaction 3

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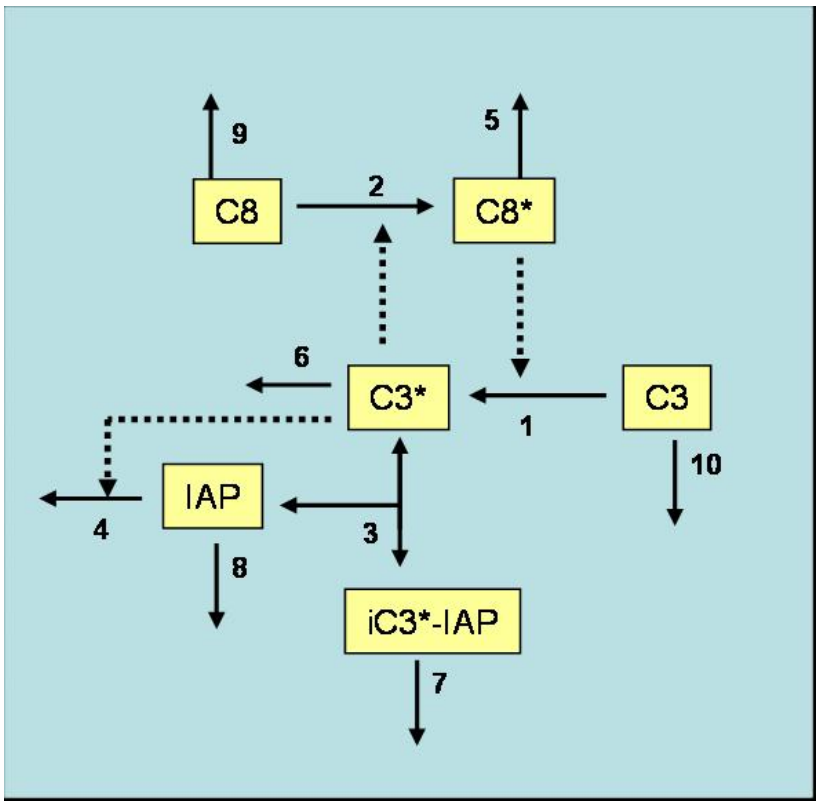
Reaction 4



Eissing *et al.* (2004) *J Biol Chem* 279(35):36892–36897

Analysis of caspase modules

Extrinsic C8/C3 module: basic model

- Basic model: no IAP, only mutual positive feedback of C8 and C3.

Analysis of caspase modules

Extrinsic C8/C3 module: basic model

- Basic model: no IAP, only mutual positive feedback of C8 and C3.

Equilibrium analysis

- Two steady states: one is $[C3^*] = 0$ (unstable)
- No bistability; sensitive to perturbations

Analysis of caspase modules

Extrinsic C8/C3 module: full Eissing model

- Full model: C8/C3 feedback with IAP and C3*-IAP

Analysis of caspase modules

Extrinsic C8/C3 module: full Eissing model

- Full model: C8/C3 feedback with IAP and C3*-IAP

Equilibrium analysis

- Three steady states: one is $[C3^*] = 0$
- Possible bistability

Analysis of caspase modules

Extrinsic C8/C3 module: full Eissing model

- Full model: C8/C3 feedback with IAP and C3*-IAP

Equilibrium analysis

- Three steady states: one is $[C3^*] = 0$
- Possible bistability
- For biologically relevant parameters, two other steady states are negative

Analysis of caspase modules

Extrinsic C8/C3 module: extended Eissing model

- Extended model: additional effect of BAR

$$C8^* + BAR \rightleftharpoons C8^*BAR$$

Analysis of caspase modules

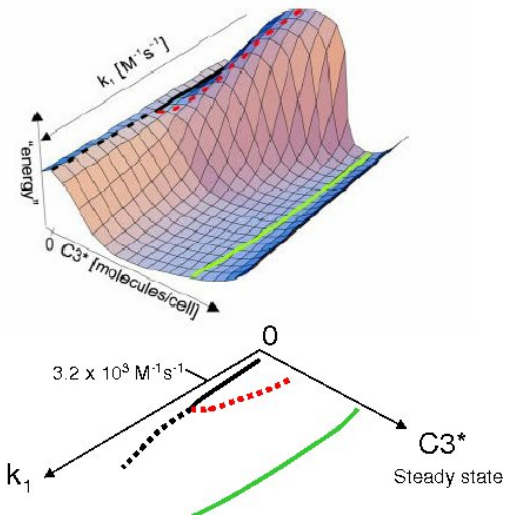
Extrinsic C8/C3 module: extended Eissing model

- Extended model: additional effect of BAR

$$C8^* + BAR \rightleftharpoons C8^*BAR$$

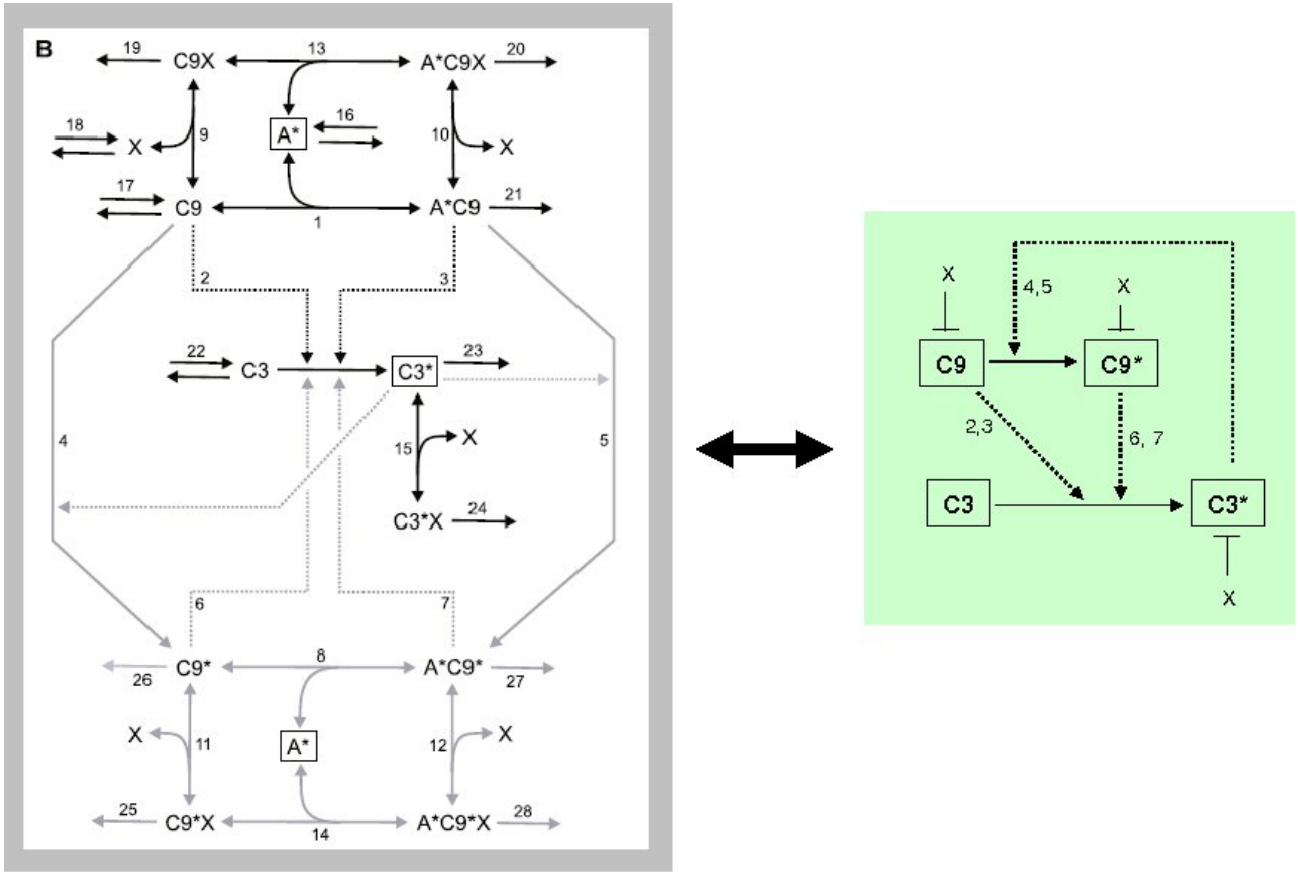
Equilibrium analysis

- Five steady states: one is $[C3^*] = 0$
- Bistability with three non-negative states for biological parameters
- Intuitively, need thresholds on both C3 and C8



Analysis of caspase modules

Intrinsic C9/C3 module: Legewie model

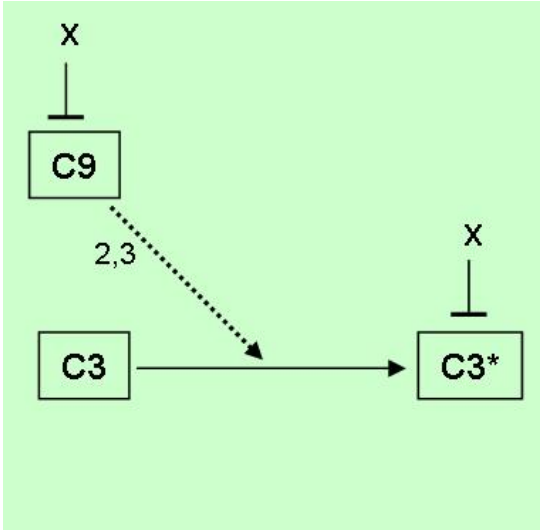


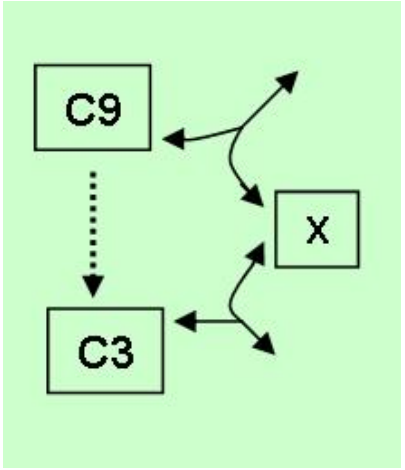
Wild-type Model
Legewie et al. (2006)

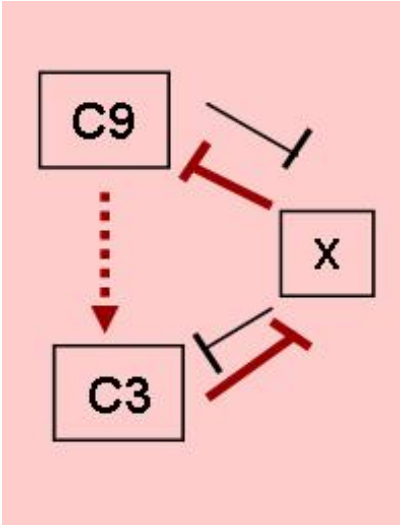
Dynamics are similar to Eissing model

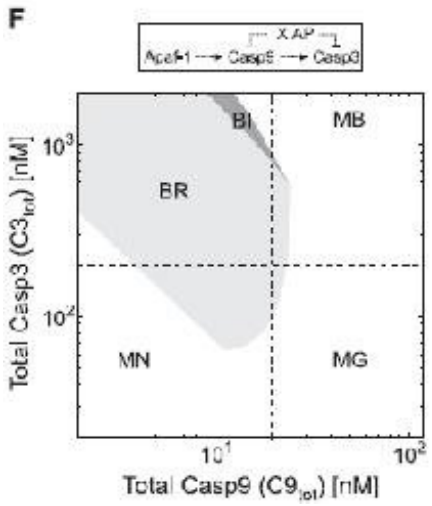
Analysis of caspase modules

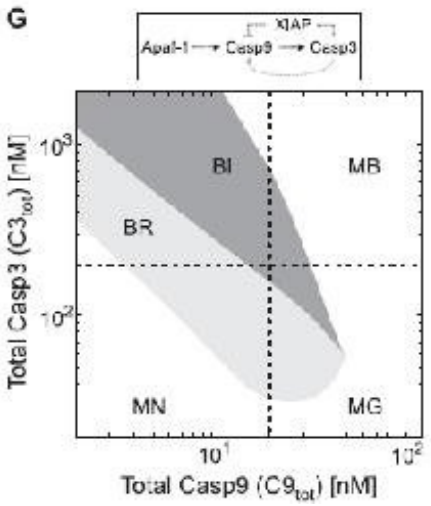
Intrinsic C9/C3 module: bistability through IAP

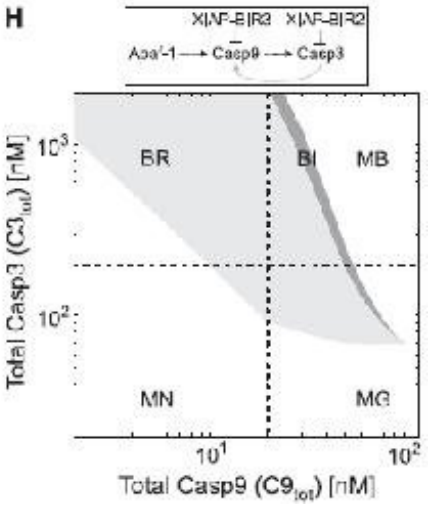






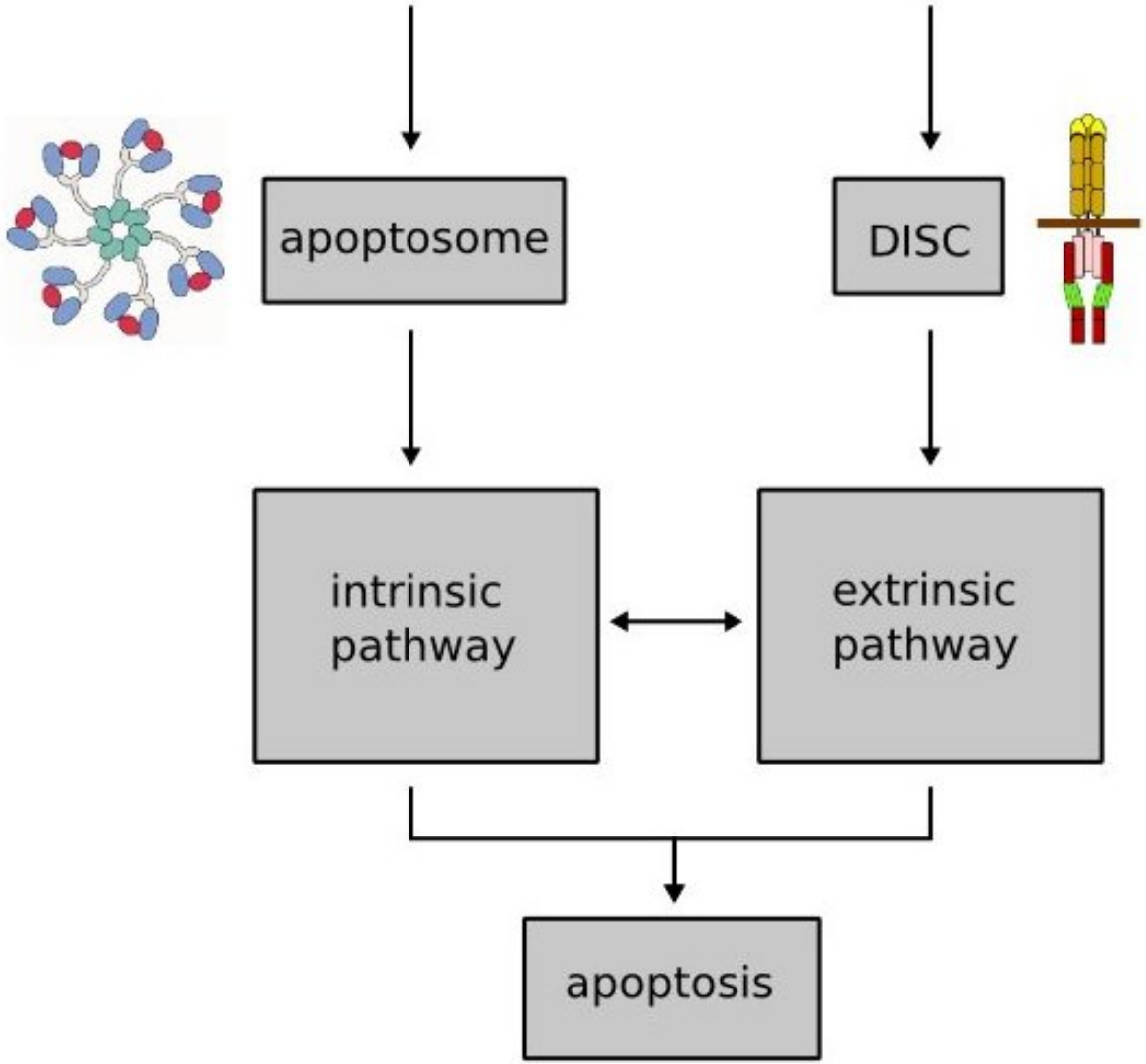






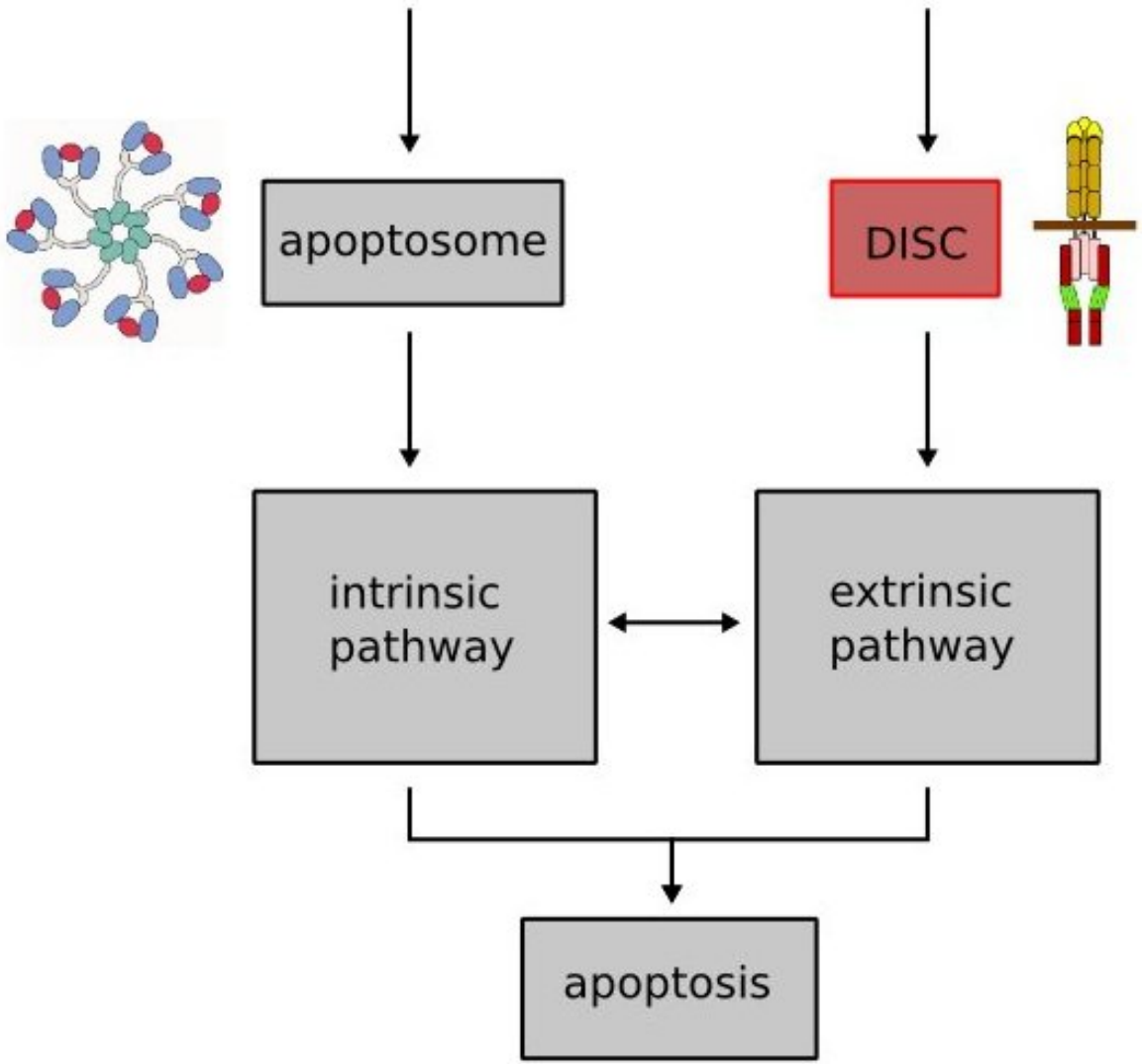
Oligomerization kinetics

Modularization of network



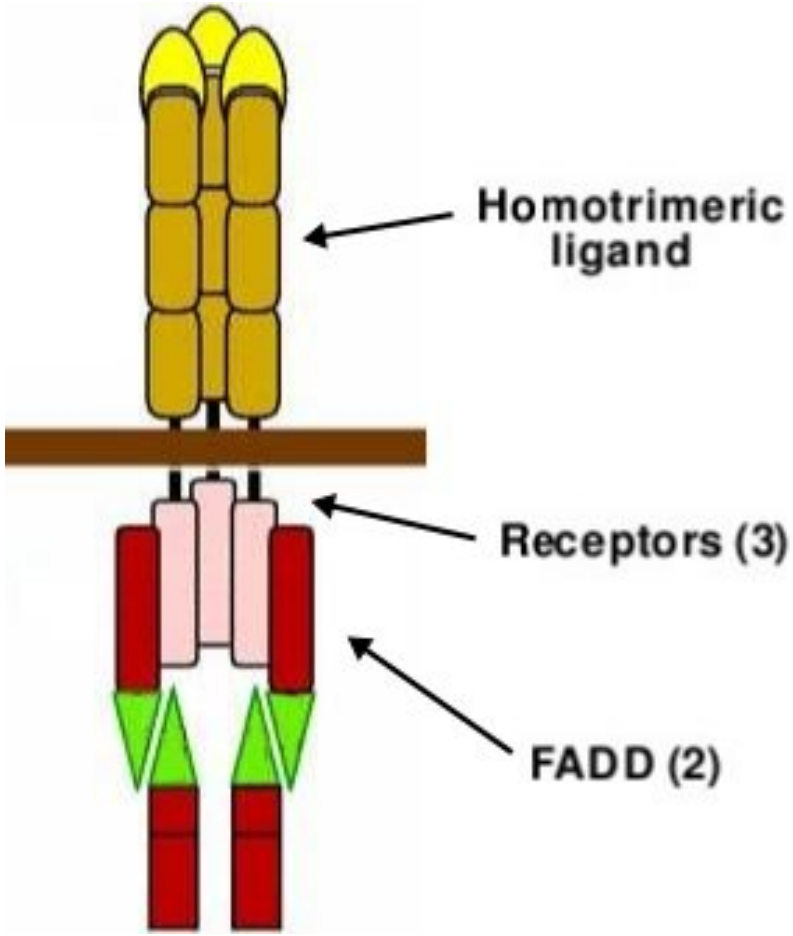
Oligomerization kinetics

DISC module



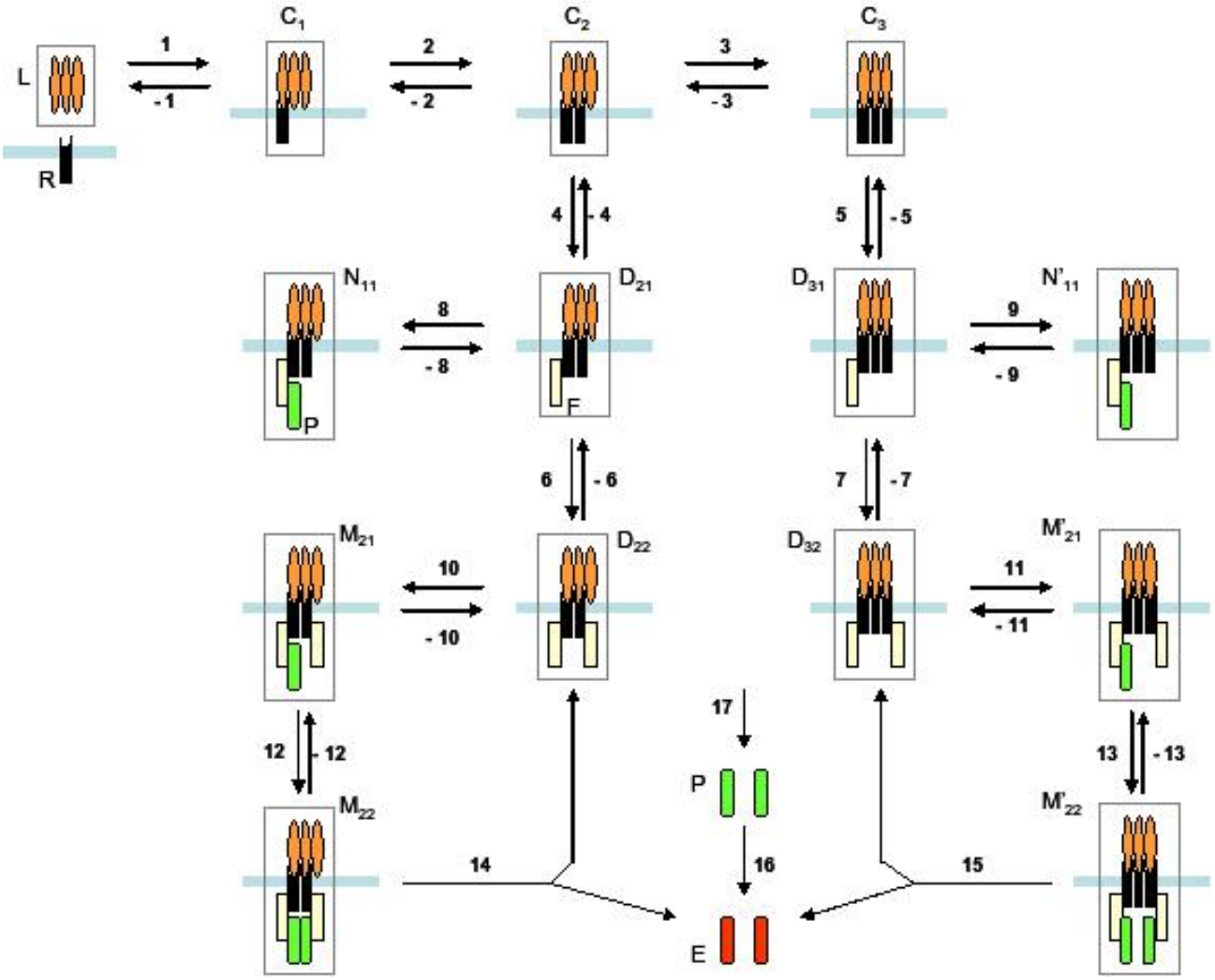
Oligomerization kinetics

DISC module: formation



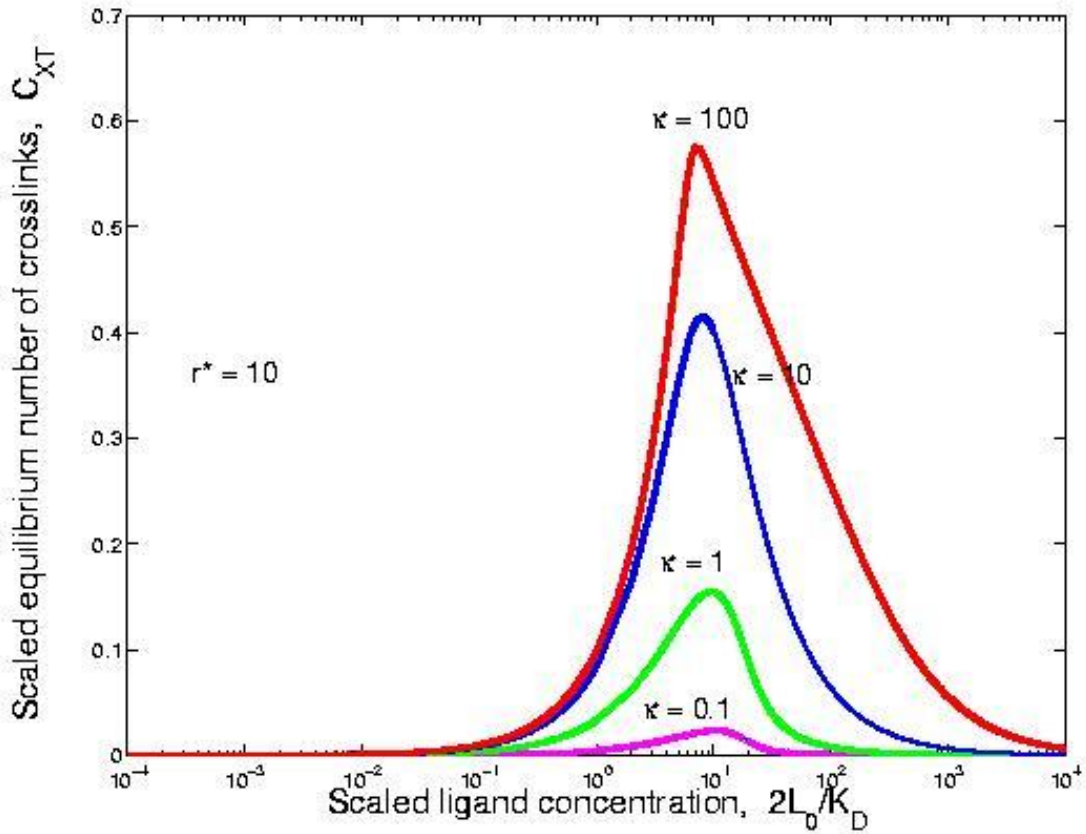
Oligomerization kinetics

DISC module: Lai-Jackson model



Oligomerization kinetics

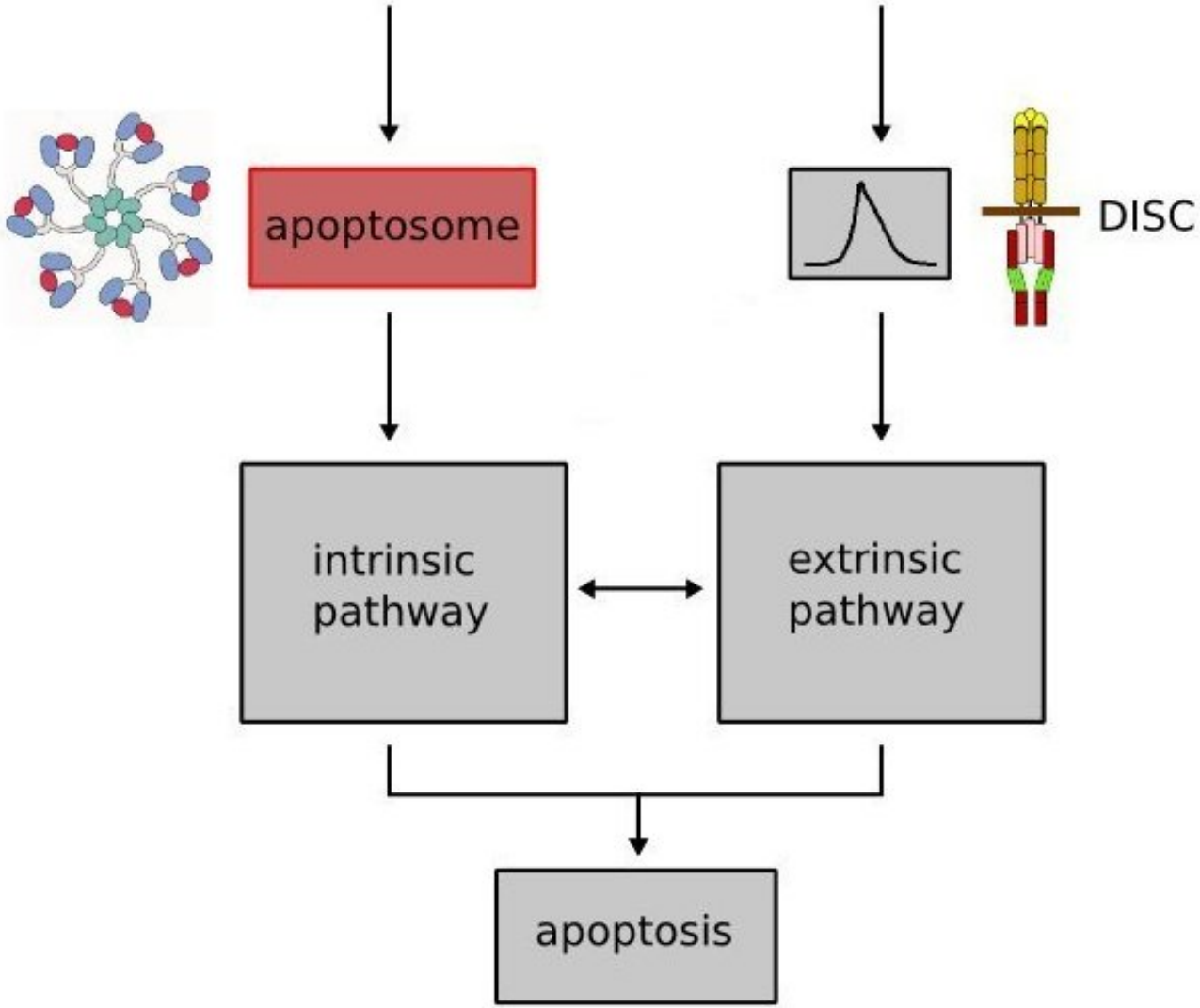
DISC module: Lai-Jackson solution



Lai R, Jackson TL (2004) *Math Biosci Eng* 1(2):325–338

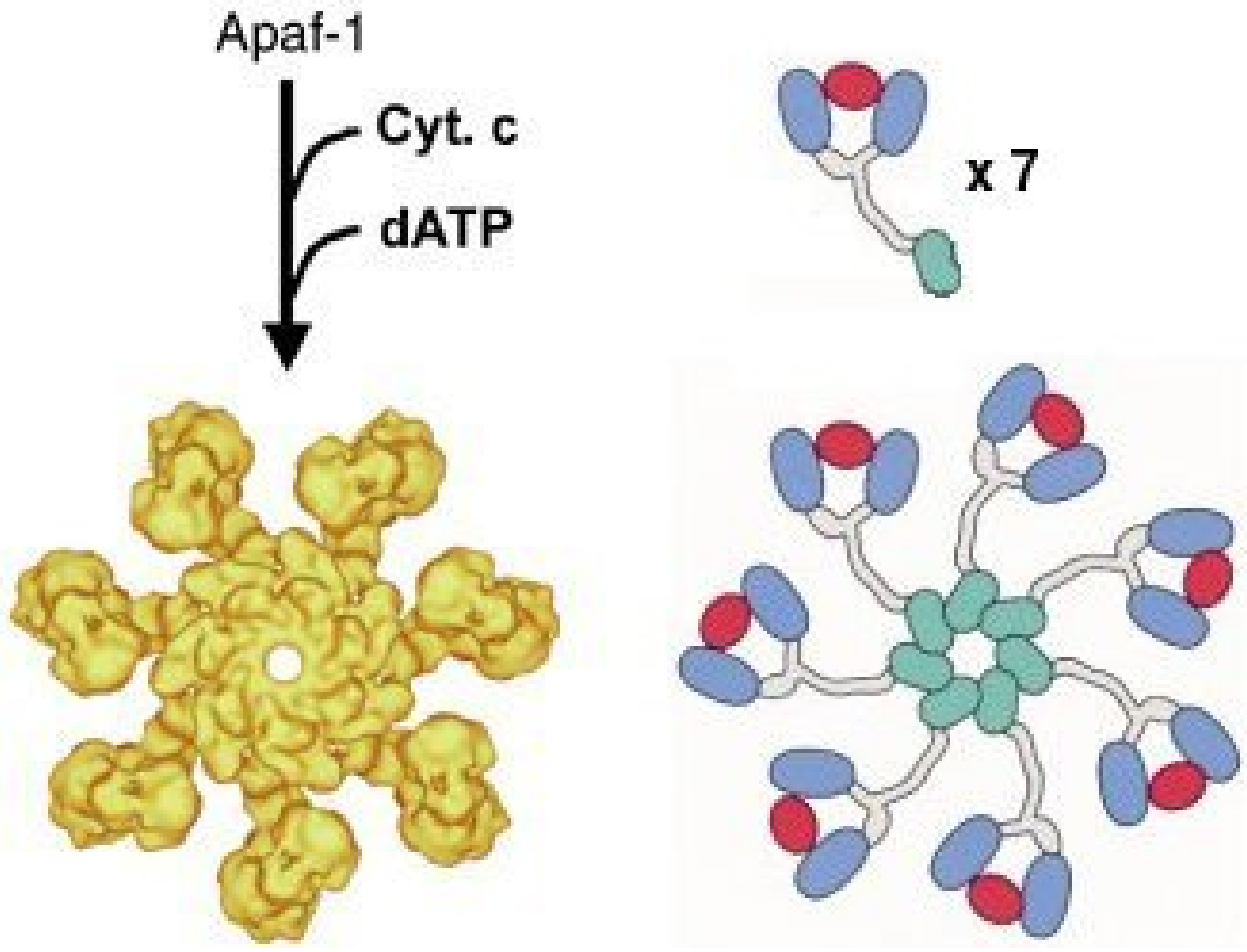
Oligomerization kinetics

Apoptosome module



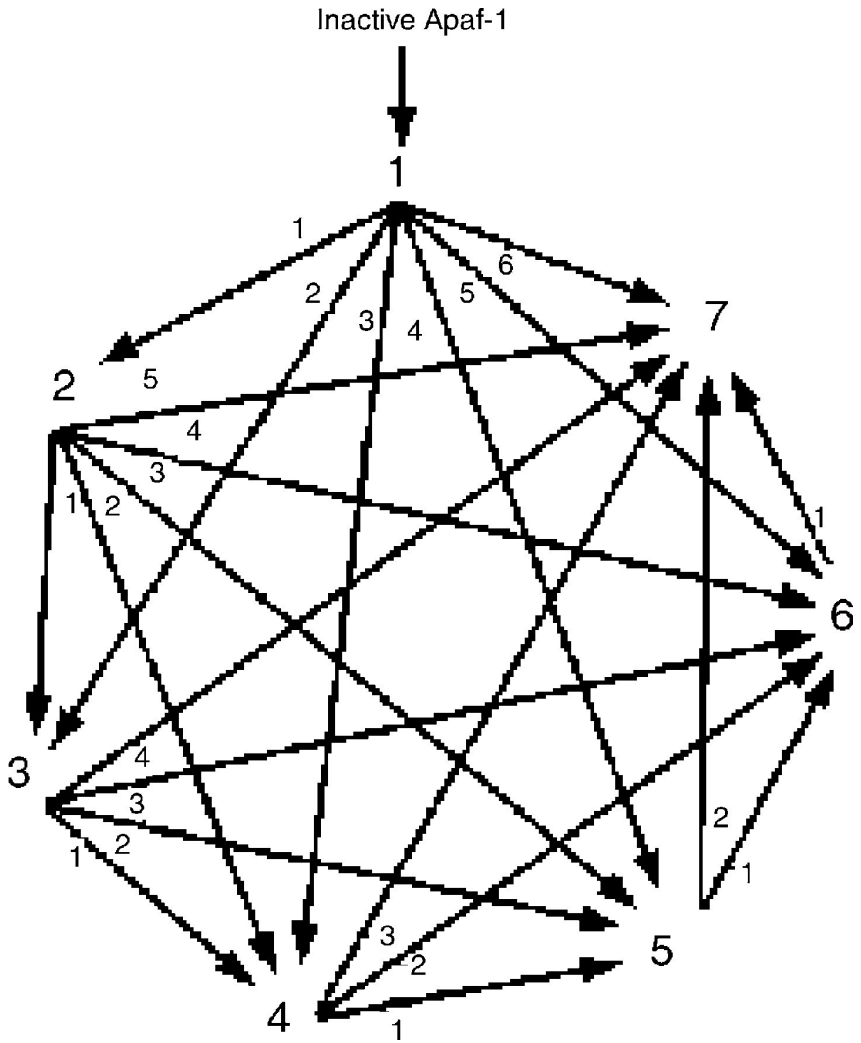
Oligomerization kinetics

Apoptosome module: formation



Oligomerization kinetics

Apoptosome module: Nakabayashi-Sasaki model



Association

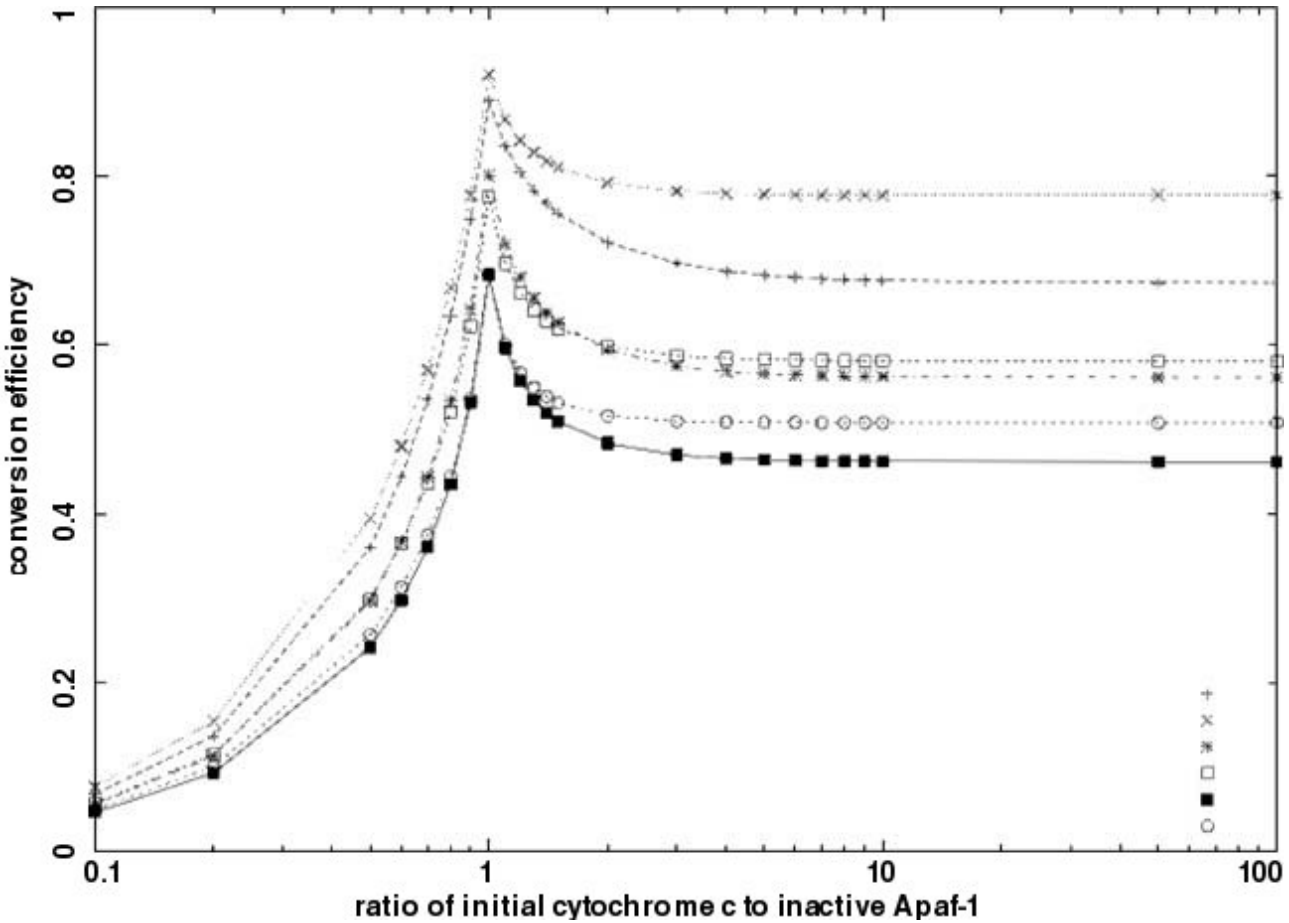
$$x_i + x_j \longrightarrow x_{i+j},\ i + j \leq 7$$

Dissociation

$$x_k \longrightarrow x_i + x_j,\ i + j = k$$

Oligomerization kinetics

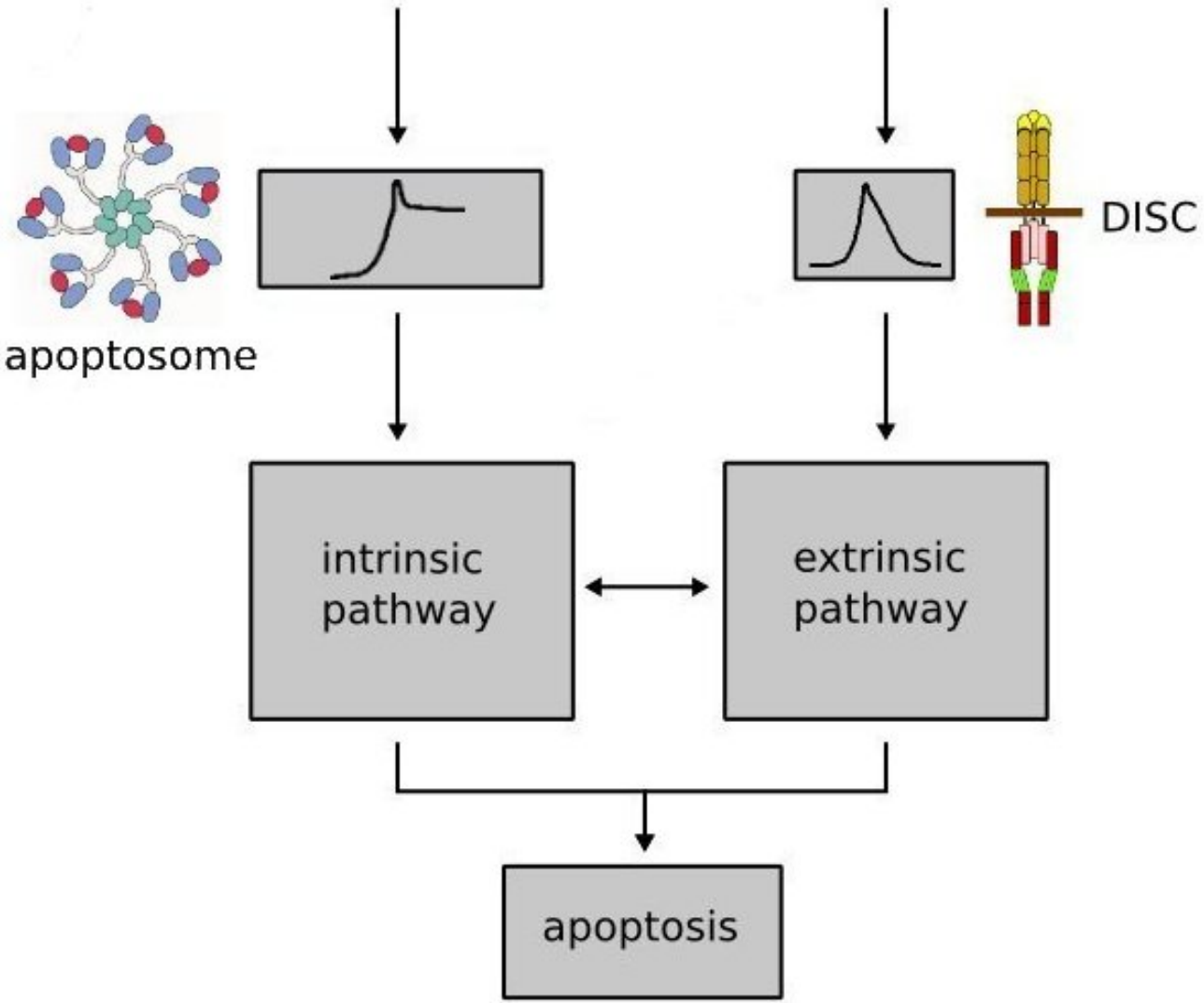
Apoptosome module: Nakabayashi-Sasaki solution



Nakabayashi J, Sasaki A (2006) *J Theor Biol* 242:280–287

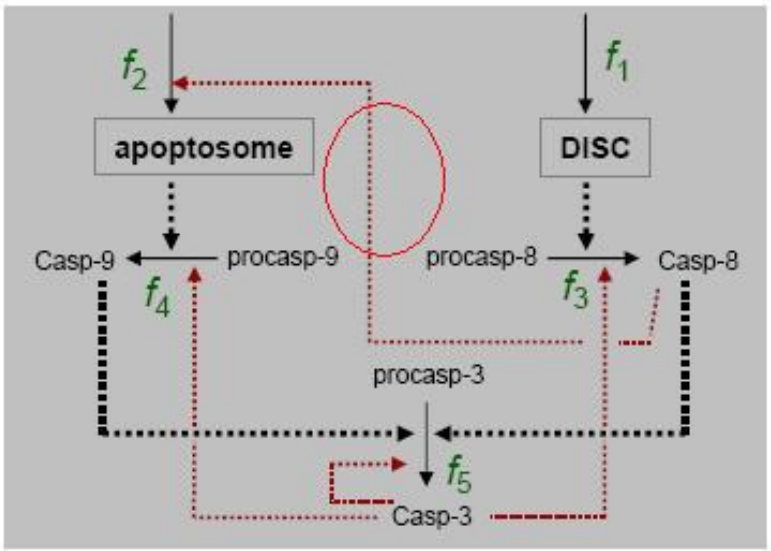
Oligomerization kinetics

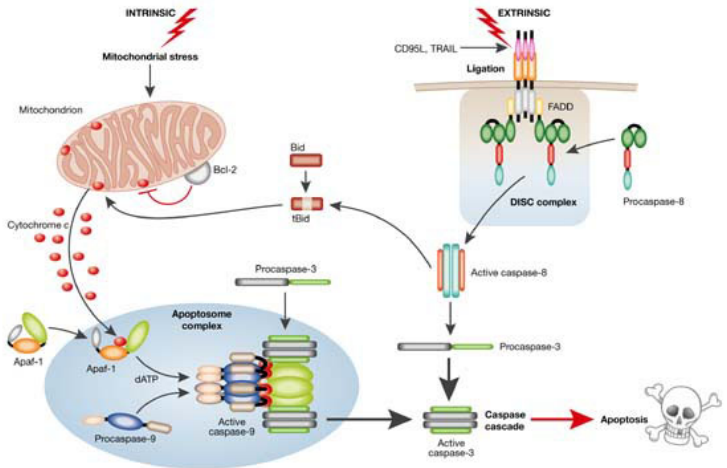
Module abstraction



Combined model

Module integration: connection through Bid

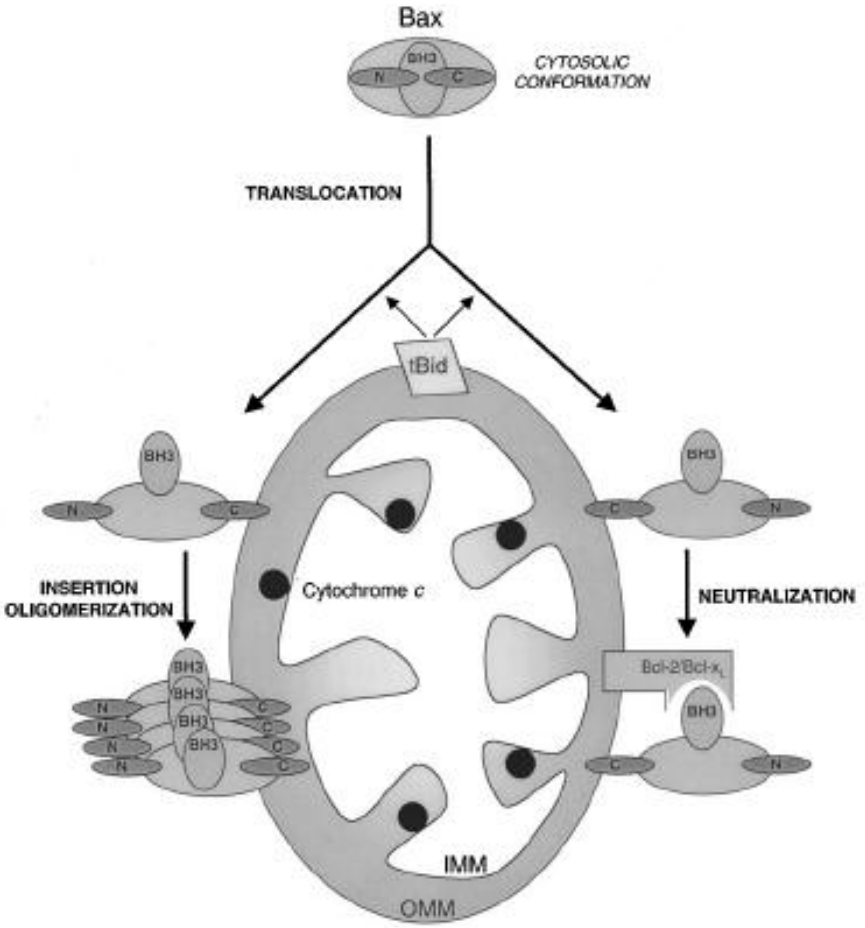




Apoptosis and disease: a life or death decision.
EMBO Rep. 2004 Jul;5(7):674-8. Epub 2004 Jun 25.

Combined model

Module integration: Bax oligomerization releases cytochrome *c*



Bid drives this irreversible process.

Combined model

Dynamical equations: extrinsic pathway

$$
\begin{aligned}
[\dot{D}] &= v_1 - \mu_D [D] \\
[\dot{C8}] &= -v_2 + \alpha_{C8} - \mu_{C8} [C8] \\
[\dot{C8a}] &= v_2 - v_{11} - \mu_{C8a} [C8a] \\
[\dot{C3}] &= -v_3 + \alpha_{C3} - \mu_{C3} [C3] \\
[\dot{C3a}] &= v_3 - v_4 - \mu_{C3a} [C3a] \\
[\dot{IAP}] &= -v_4 - v_5 - v_{10} + \alpha_{IAP} - \mu_{IAP} [IAP] \\
[\dot{C3aIAP}] &= v_4 - \mu_{C3aIAP} [C3aIAP] \\
[\dot{BAR}] &= -v_{11} + \alpha_{BAR} - \mu_{BAR} [BAR] \\
[\dot{C8aBAR}] &= v_{11} - \mu_{C8aBAR} [C8aBAR]
\end{aligned}
$$

Combined model

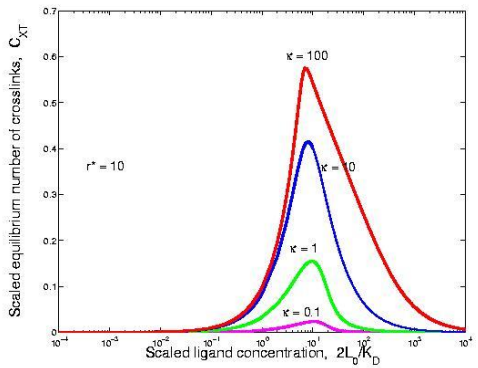
Dynamical equations: intrinsic pathway

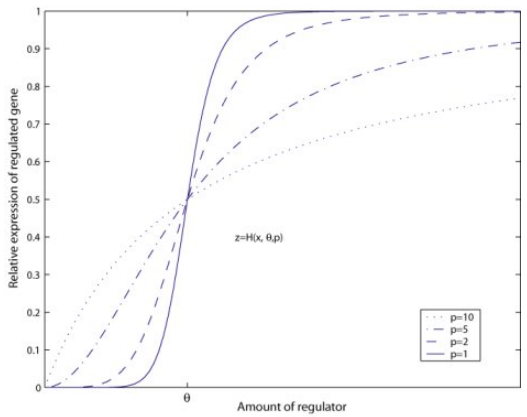
$$
\begin{aligned}
\dot{[cytC]} &= v_7 - v_8 - \mu_{cytC}\,[cytC] \\
\dot{[A]} &= v_8 - \mu_A\,[A] \\
\dot{[C9]} &= -v_9 + \alpha_{C9} - \mu_{C9}\,[C9] \\
\dot{[C9a]} &= v_9 - v_{10} - \mu_{C9a}\,[C9a] \\
\dot{[C9aIAP]} &= v_{10} - \mu_{C9aIAP}\,[C9aIAP] \\
\dot{[Bid]} &= -v_6 + \alpha_{Bid} - \mu_{Bid}\,[Bid] \\
\dot{[C8aBid]} &= v_6 - \mu_{C8aBid}\,[C8aBid]
\end{aligned}
$$

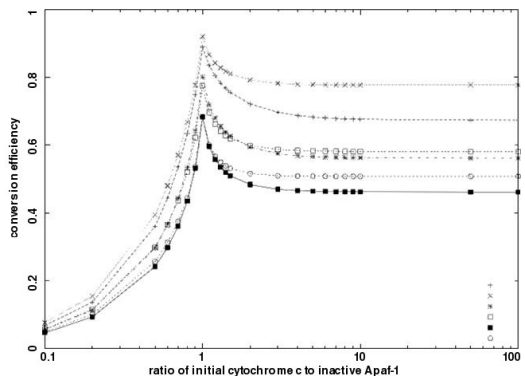
Combined model

Dynamical equations: modularization

- DISC module: $v_1 = k_1 f_D(l_0, r_0)$
- Bid connection: $v_7 = \frac{k_7 [C8aBid]^{n_7}}{K_{m7}^{n_7} + [C8aBid]^{n_7}}$
- Apoptosome module: $v_8 = k_8 f_A([cytC], a_0)$

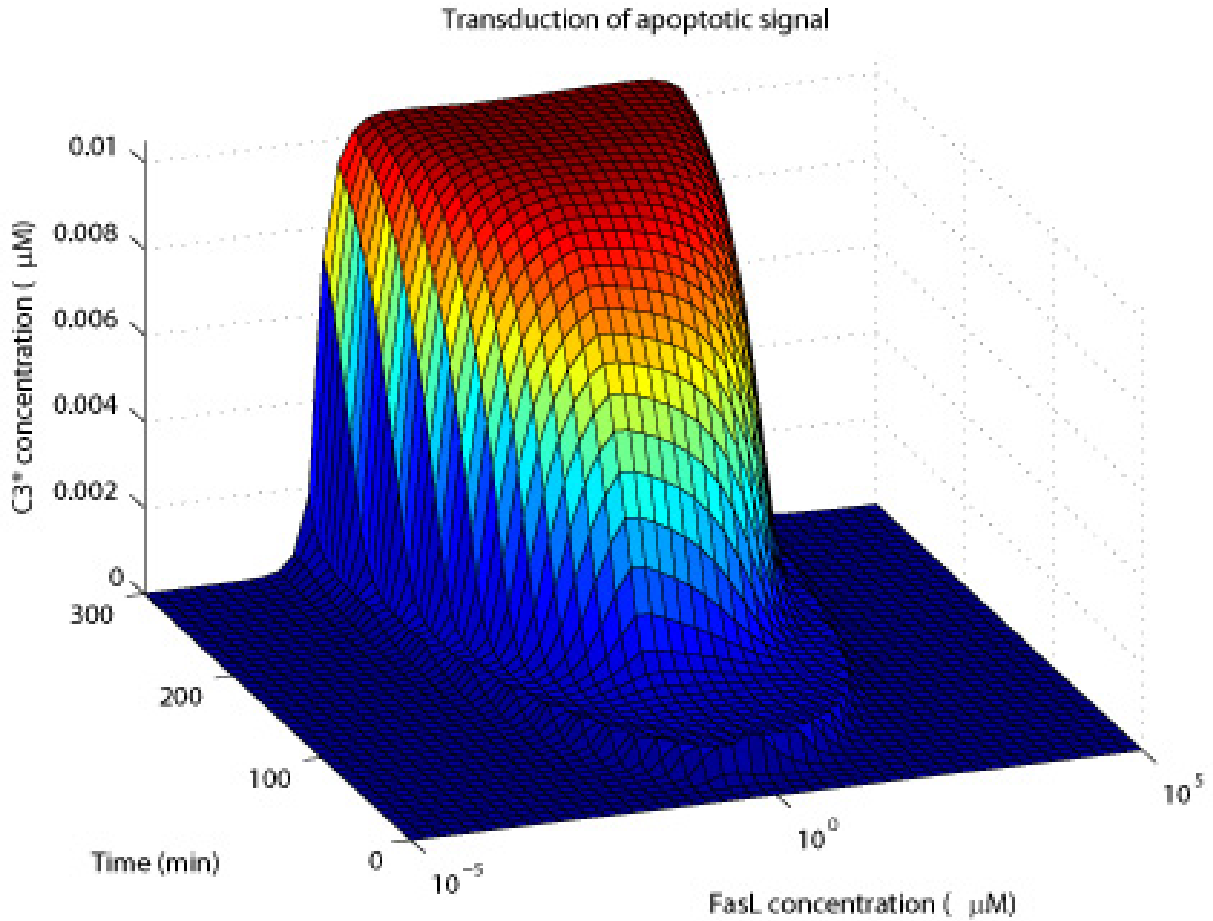






Combined model

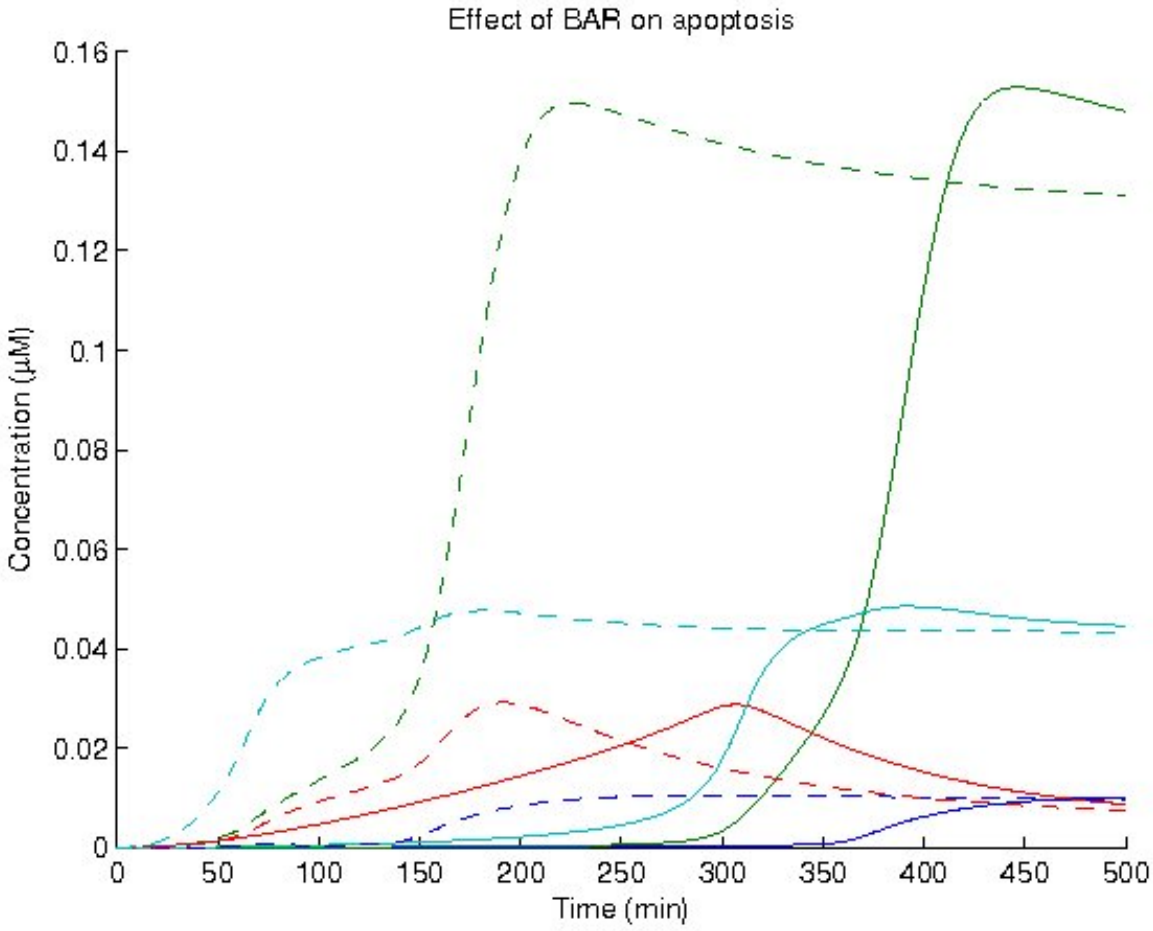
Simulation results: caspase-3 activation is a function of ligand and time



There is a range of ligand that solicits maximum caspase-3 activation.

Combined model

Simulation results: BAR inhibits caspase-8 to prevent accidental activation of apoptosis



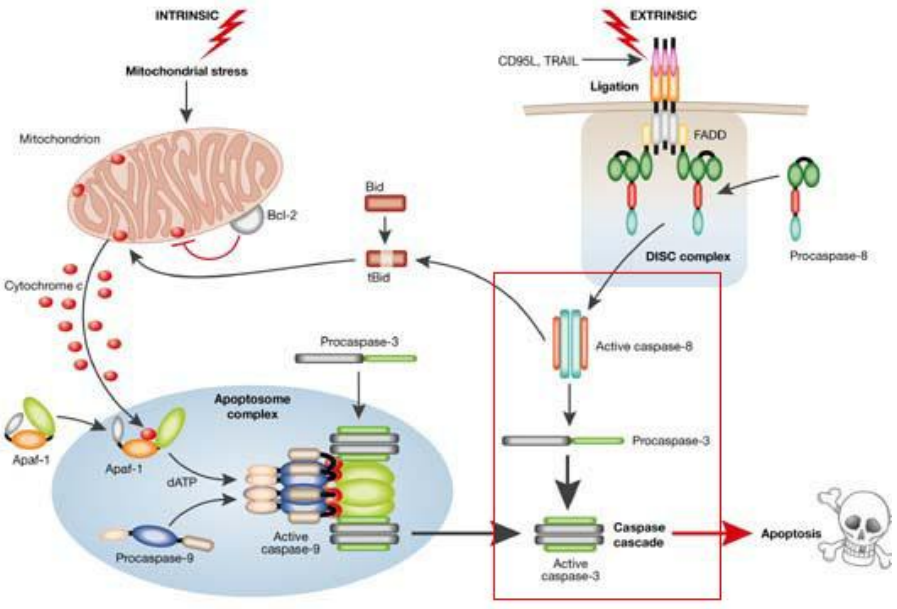
- Blue: C3*
- Green: C9*
- Red: C3*-IAP
- Cyan: C9*-IAP

Dashed lines: weaken C8*-BAR formation by rate constant: earlier onset.

Inhibition of caspase-8 prevents sub-threshold receptor-ligand interaction.

Combined model

Simulation results: extrinsic pathway alone has limited impact to peak caspase-3 activity



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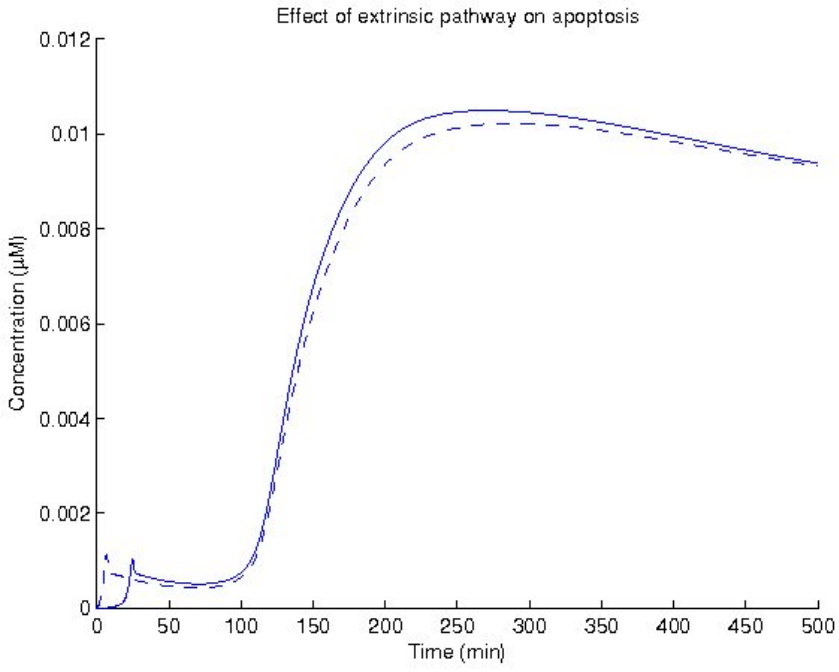
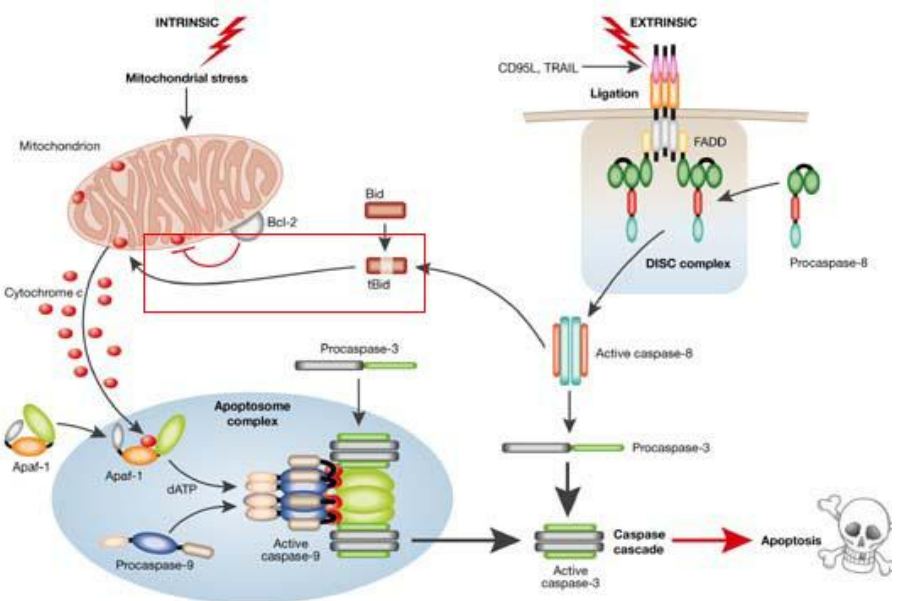


Changing rate constant for activation by caspase-8 (thus extrinsic pathway) did not impact caspase-3 activity.

Combined model

Simulation results: cytochrome *c* amplifies caspase-3 activation



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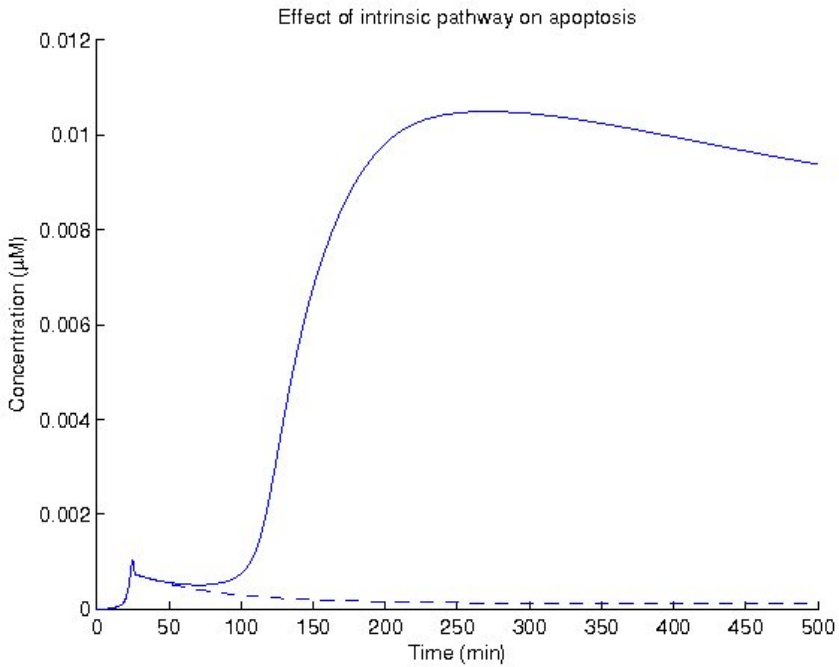
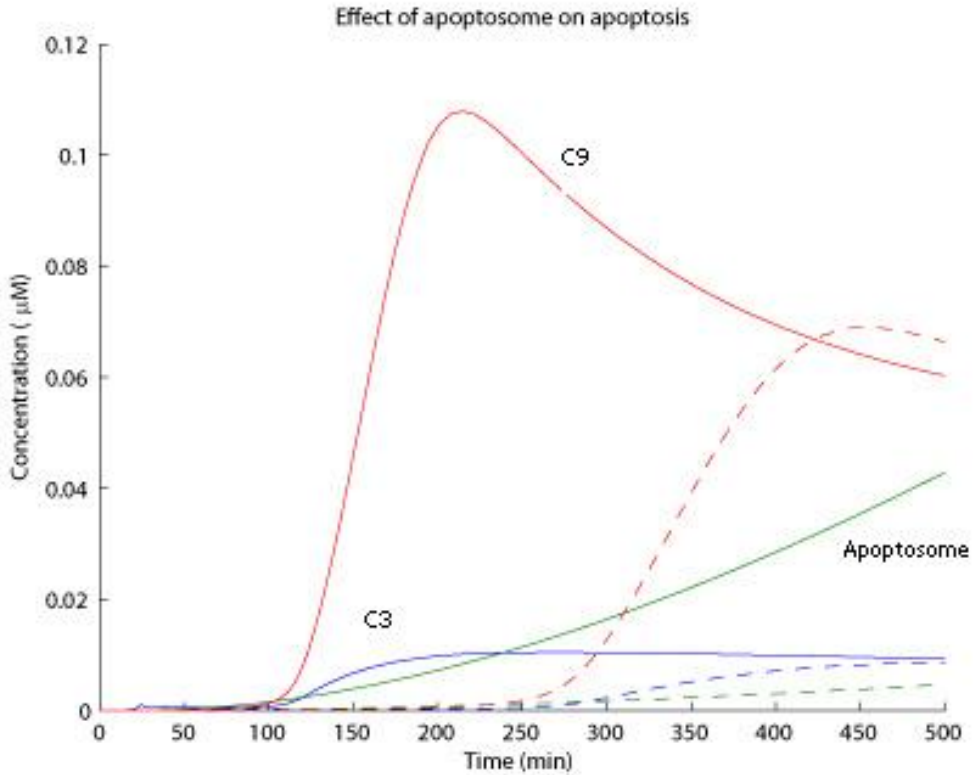
EMBO Rep. 2004 Jul;5(7):674-8. Epub 2004 Jun 23.



Blocking of cytochrome *c* release suppresses apoptosis.

Combined model

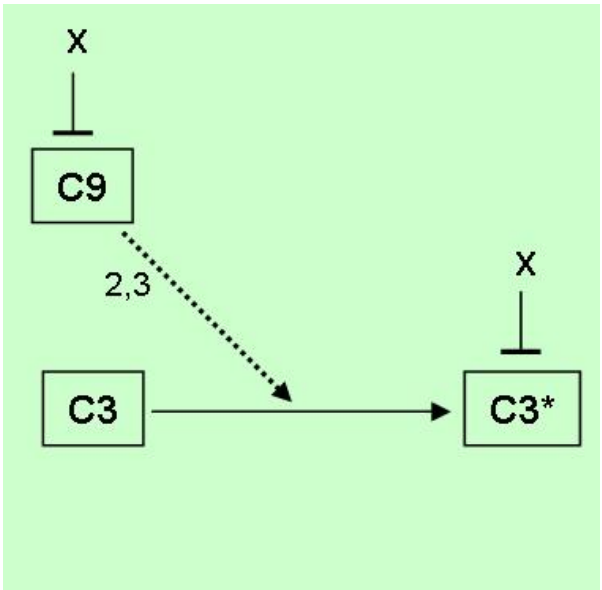
Simulation results: caspase-3 activation involves apoptosome assembly and caspase-9

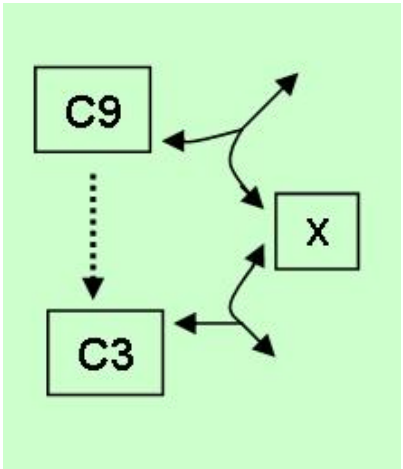


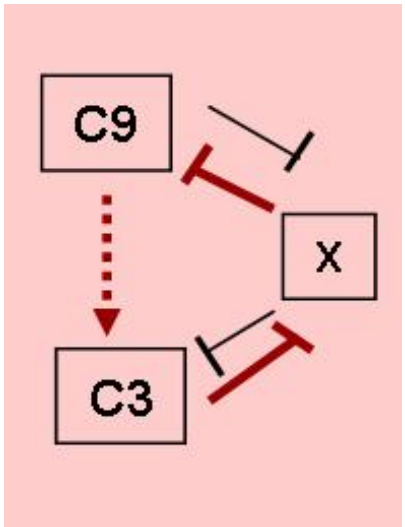
- Reducing rate of apoptosome formation delays onset of caspase-3 activation.
- Caspase-9 activation precedes caspase-3 activation.
- What is the mechanism by which caspase-9 activates caspase-3?

Combined model

Simulation results: IAP antagonists enhance caspase-3 activation (1)



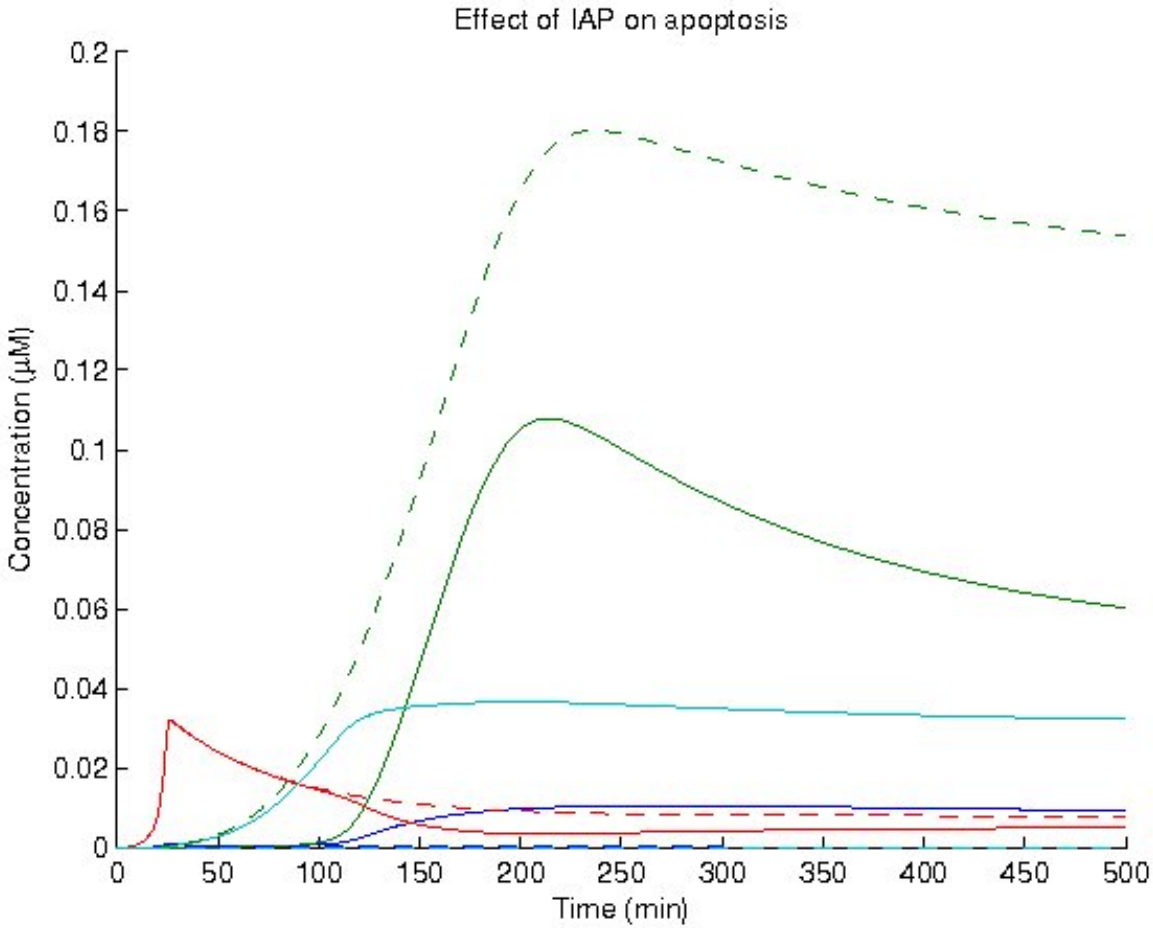




- In our model, caspase-9 competes for IAP against caspase-3.
- Caspase-9 relieves IAP suppression of caspase-3.
- Real example: Smac mimic potentiates caspase-3 activation. Science 3 September 2004: Vol. 305, no. 5689, pp. 1471–1474

Combined model

Simulation results: IAP antagonists enhance caspase-3 activation (2)



- Blue: $C3^*$
- Green: $C9^*$
- Red: $C3^*$-IAP
- Cyan: $C9^*$-IAP

Dashed lines: shut down $C9^*$-IAP formation reaction.

No $C9^*$-IAP, no $C3^*$.

Conclusion

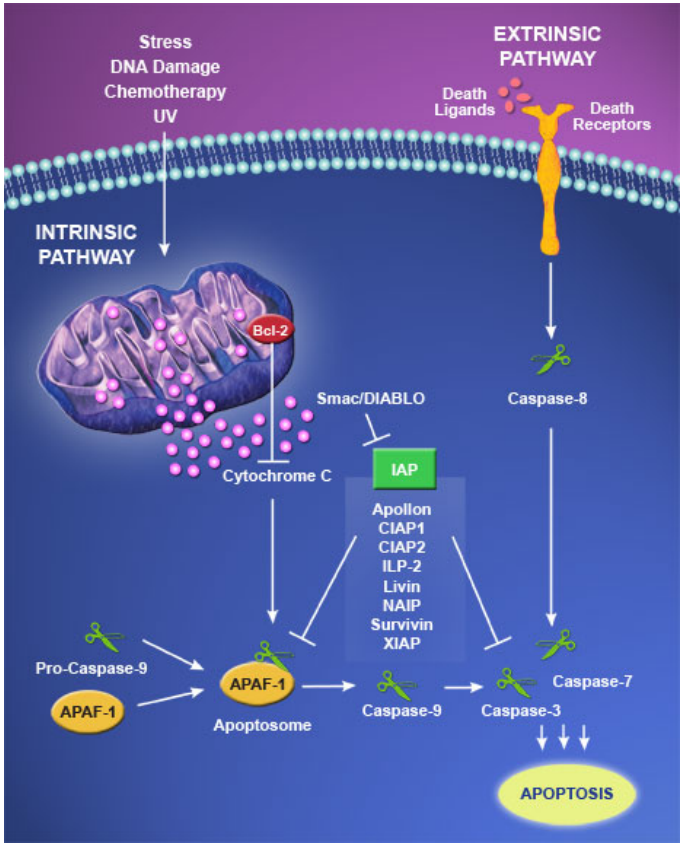
Combined model: demonstrations

- Our model demonstrates:
  1. Cytochrome *c* release resembles a point of no return.
  2. Connection between extrinsic and intrinsic pathways is required for caspase-dependent cell death.

Conclusion

Combined model: predictions

- Our model predicts:
  1. Shutting down intrinsic pathway at cytochrome *c* release will stop progression to apoptosis.
  2. Intrinsic pathway feedback (C3, C9, IAP) is a stronger initiator of apoptosis than extrinsic pathway feedback (C3, C8)
  3. Potential drug targets to induce apoptosis: BAR antagonist, IAP antagonist (Smac mimic: currently under development)



Acknowledgements

- Dr. Baltazar Aguda and Dr. Chiu-Yen Kao
- Prof. Friedman and Prof. Keener
- MBI staff and participants