Mathematical modeling of apoptosis: the death-inducing signaling complex

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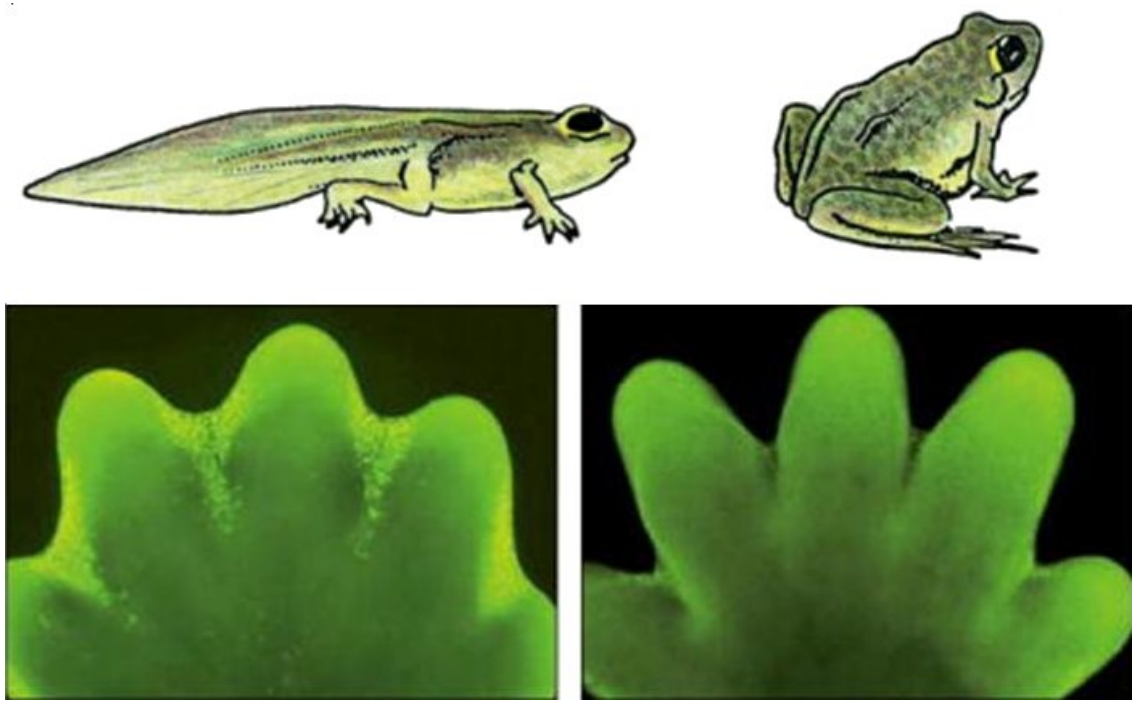
- Dysregulation associated with pathological conditions
- Characteristic cell death morphology



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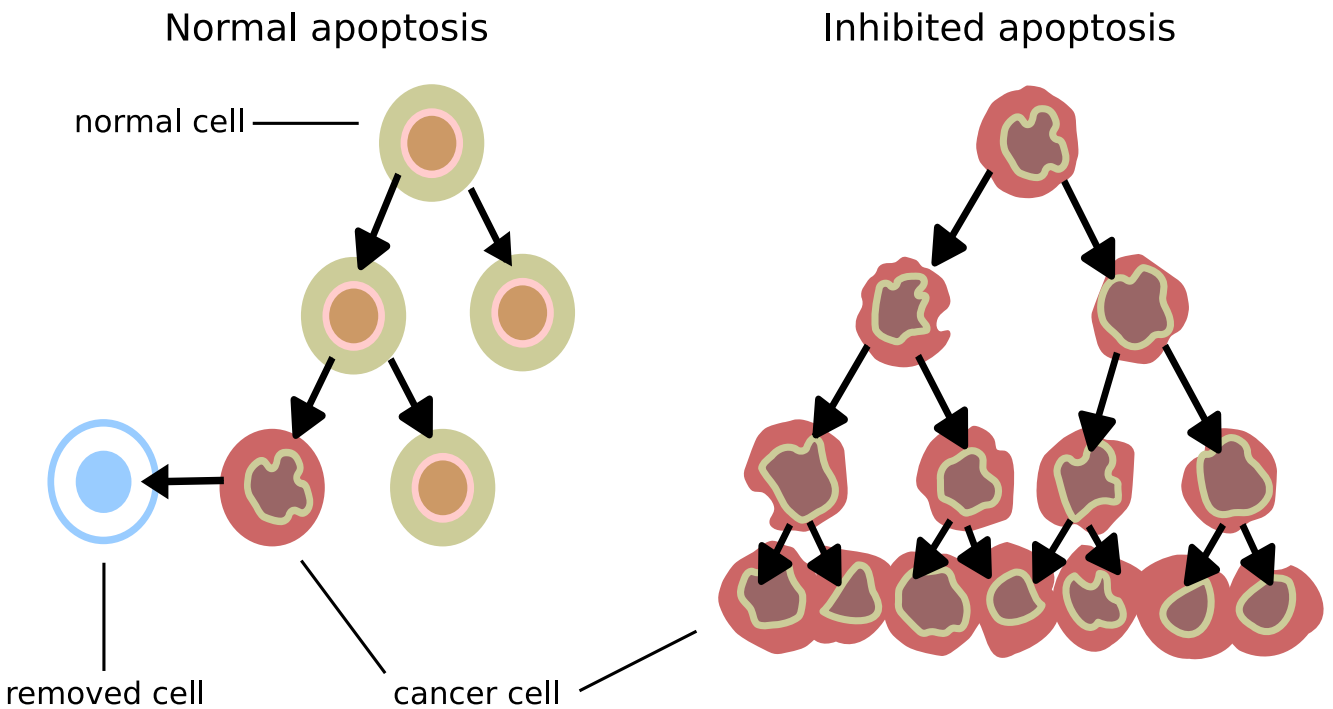

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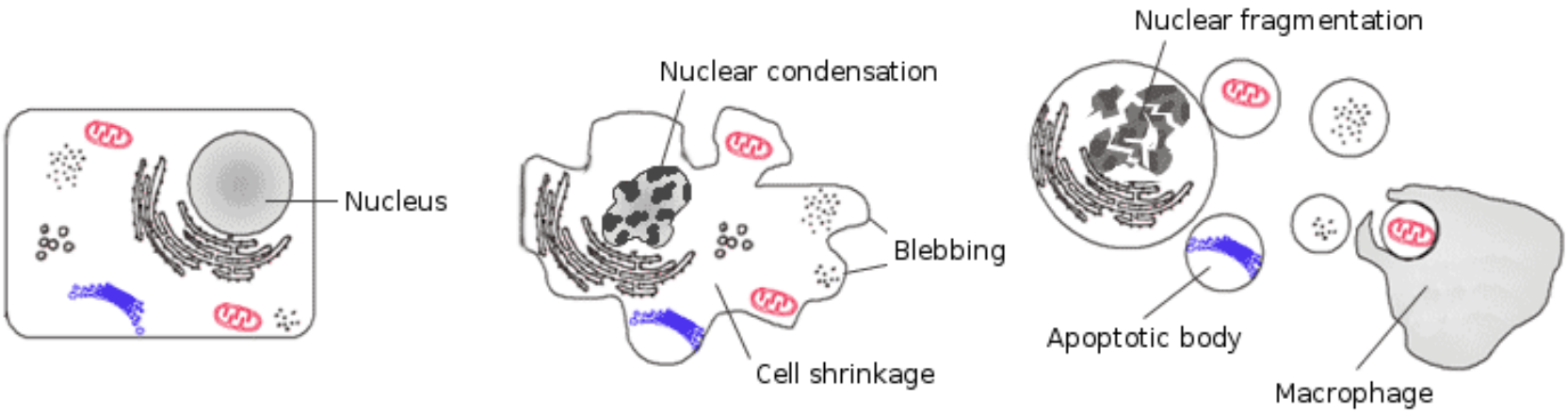
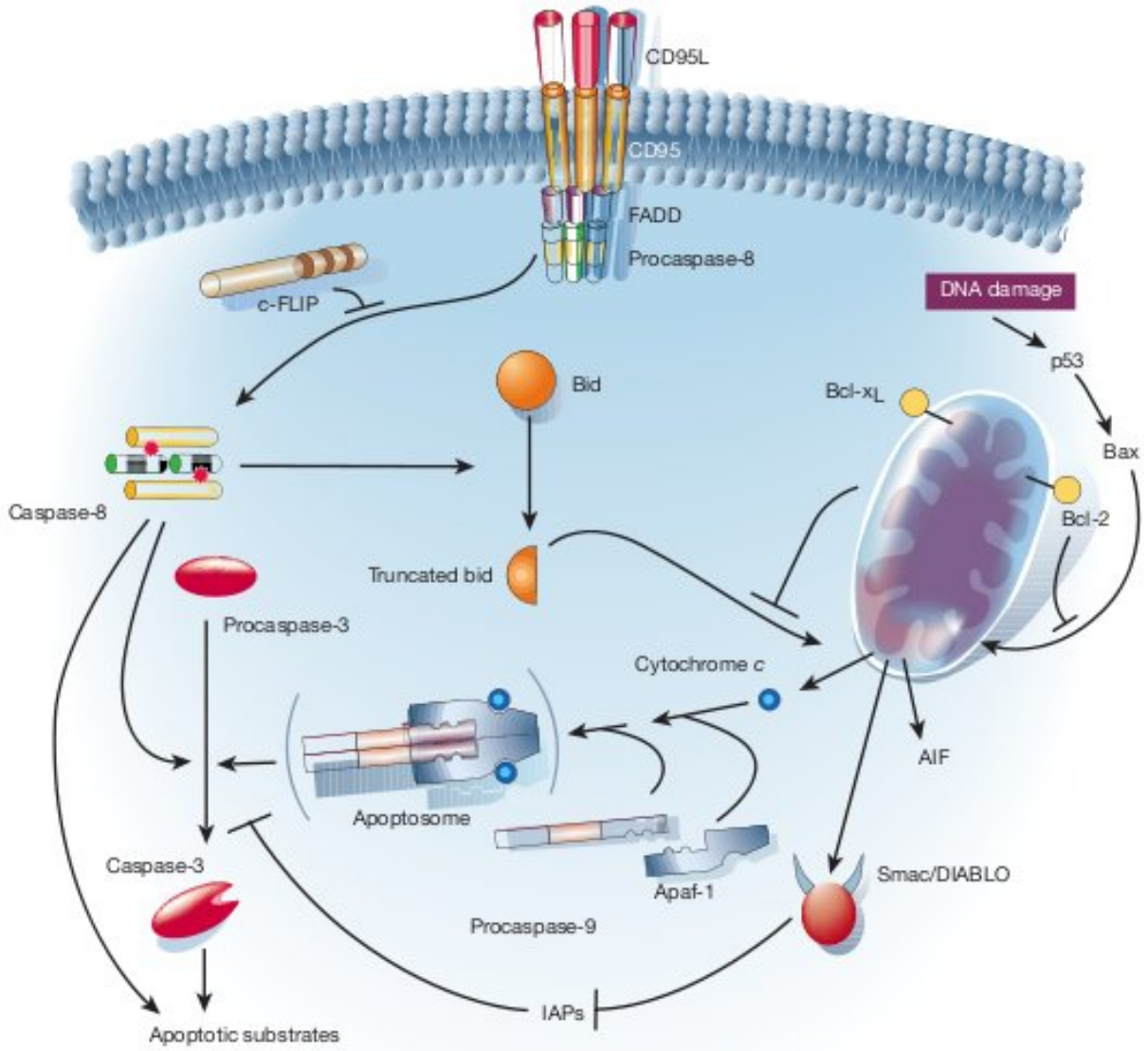


Biochemistry of apoptosis



Hengartner (2000)

Motivation for a detailed model

Previous models of apoptosis

Complete but unstable

Harrington et al. (2008)
Hua et al. (2005)
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Stable but incomplete

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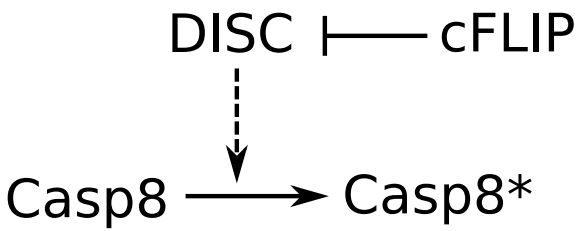
How to achieve a complete and stable model?

1. Mechanistic description of oligomerization
2. Inclusion of inhibitors (IAP, BAR, cFLIP)
3. Synthesis and degradation

Role of cFLIP: a toy model

- Toy model:



- Reactions:

$$\mathrm{DISC} + \mathrm{cFLIP} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathrm{DISC{:}cFLIP},$$

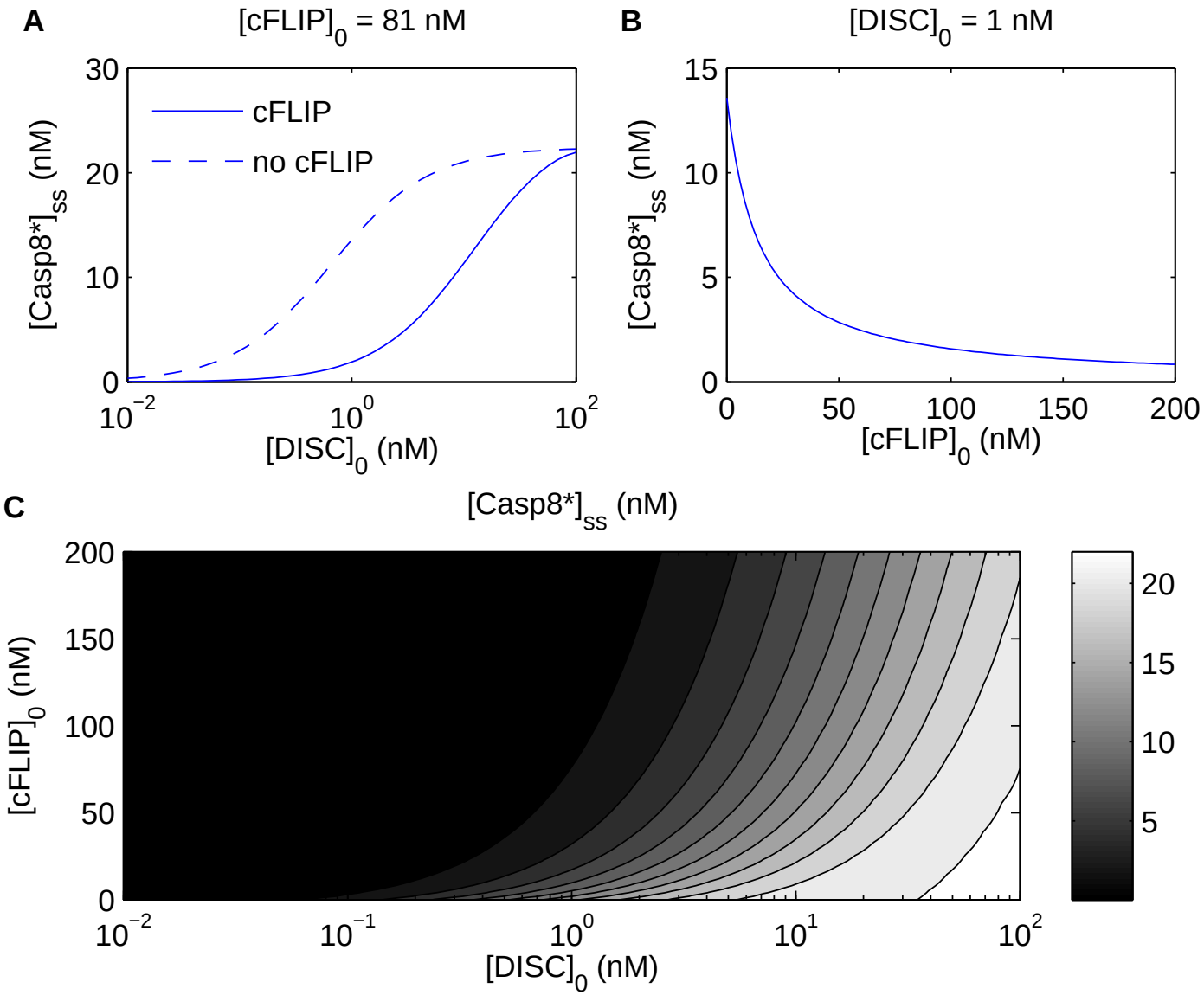
$$\mathrm{DISC} + \mathrm{Casp8} \xrightarrow{k_2} \mathrm{DISC} + \mathrm{Casp8}^*,$$

$$\emptyset \underset{\beta}{\overset{\alpha}{\rightleftharpoons}} \mathrm{Casp8} \quad , \quad \mathrm{Casp8}^* \xrightarrow{\gamma} \emptyset$$

- Steady state:

$$[\mathrm{Casp8}^*]_{\mathrm{ss}} = \frac{\alpha/\gamma}{1 + \beta/\left(k_2 \left[\mathrm{DISC}\right]_{\mathrm{ss}}\right)},$$

Role of cFLIP: a toy model



Goals

Focus on the extrinsic pathway of apoptosis

- DISC formation and its downstream interactions

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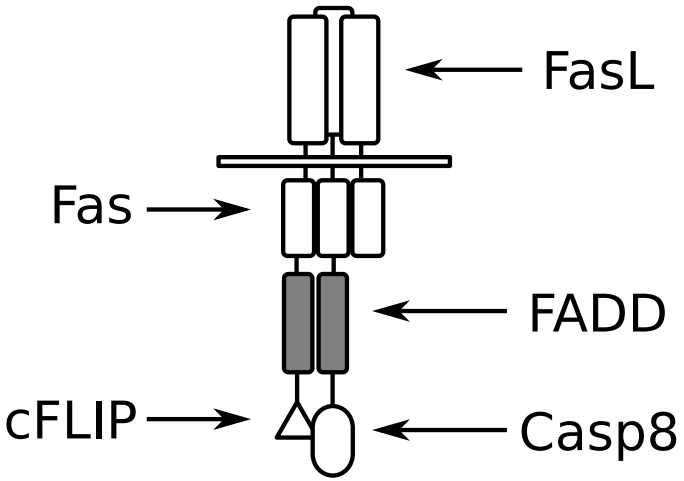
- DISC formation and its downstream interactions

Goals

1. To construct a biologically relevant model
   - Bistability at physiological parameters
   - Meaningful input-output map (FasL $\rightarrow$ Casp3*)
2. To study the function of cFLIP
   - How does it affect the apoptotic threshold?
   - Does it confer robustness to the system?

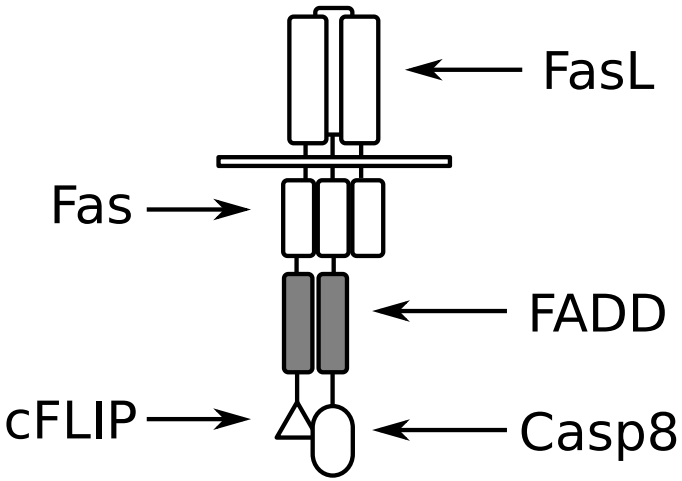
DISC model



Important features

1. Fas trimerization
2. Stepwise recruitment
3. Regulation by cFLIP
4. Pairwise Casp8 activation

DISC model



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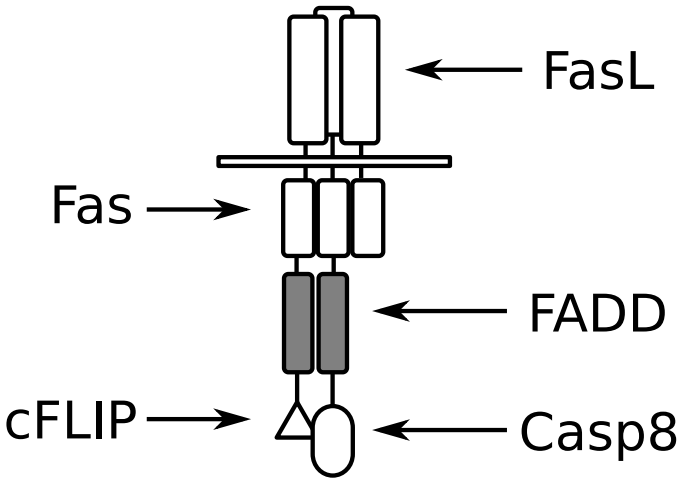
Reactions [with $(i, j, k, l) \equiv$ FasL:Fas$_i$:FADD$_j$:cFLIP$_k$:Casp8$_l$]:

$$(i,j,k,l) + \text{Fas} \rightleftharpoons (i+1,j,k,l)$$
$$(i,j,k,l) + \text{FADD} \rightleftharpoons (i,j+1,k,l)$$
$$(i,j,k,l) + \text{cFLIP} \rightleftharpoons (i,j,k+1,l)$$
$$(i,j,k,l) + \text{Casp8} \rightleftharpoons (i,j,k,l+1)$$
$$(i,j,k,l) \longrightarrow (i,j,k,l-2) + 2\text{Casp8}^*$$

DISC model



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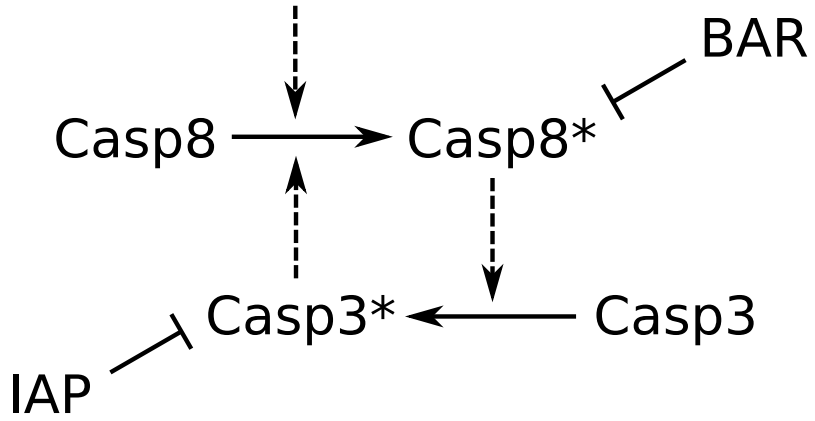
Model parameters $(\delta, \sigma_{\text{cFLIP}}, \sigma_{\text{Casp8}})$:

1. Death domain clustering ($\delta = 1,2,3$)
2. cFLIP stoichiometry ($\sigma_{\text{cFLIP}} = 1,2,3$)
3. Casp8 stoichiometry ($\sigma_{\text{Casp8}} = 2,3$)

Extrinsic caspase model

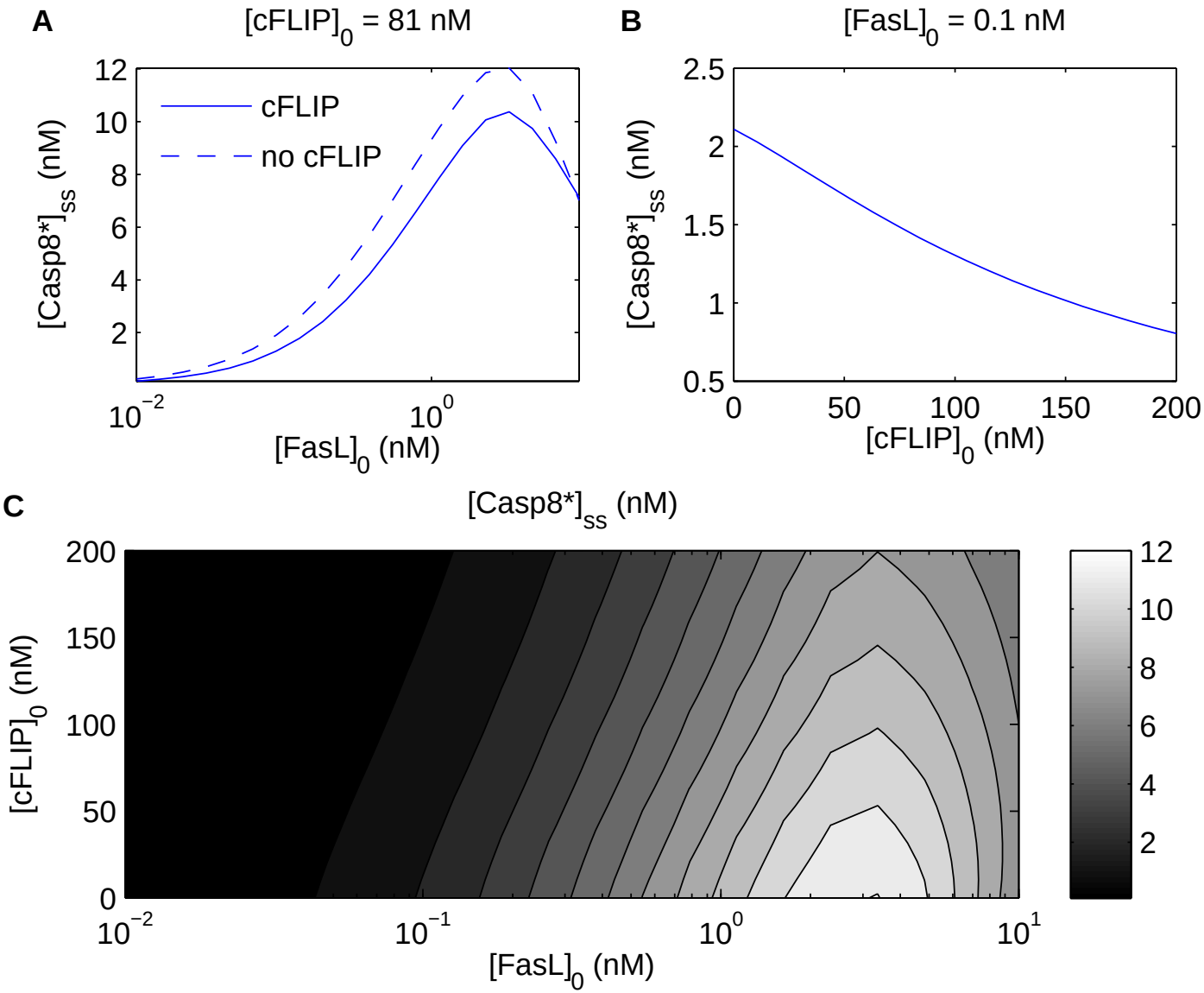
- Couple to DISC model, map from Casp8 $\longrightarrow$ Casp3:



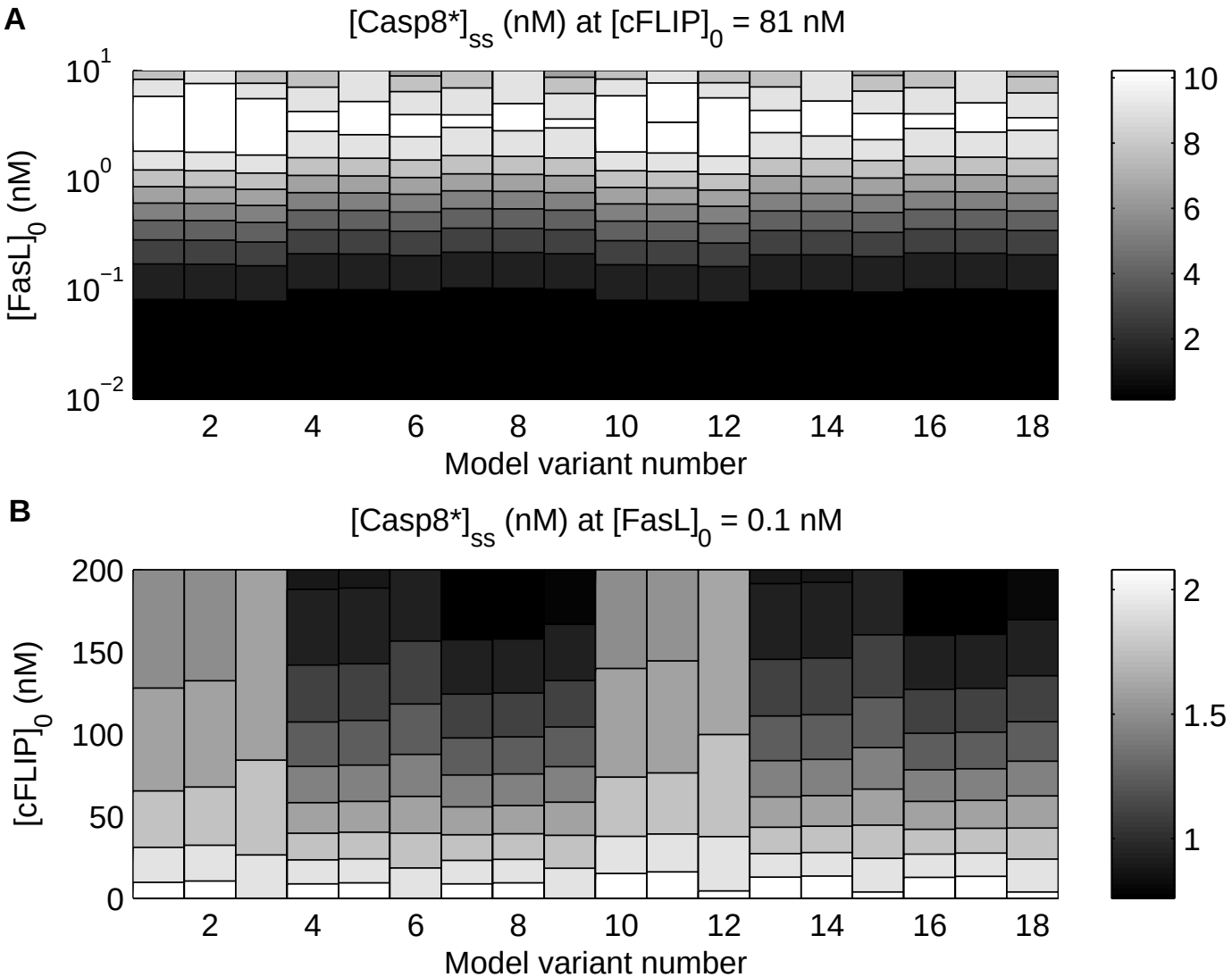
- Reactions:

$$\mathrm{Casp8^* + Casp3 \longrightarrow Casp8^* + Casp3^*}$$
$$\mathrm{Casp3^* + Casp8 \longrightarrow Casp3^* + Casp8^*}$$
$$\mathrm{Casp8^* + BAR \rightleftharpoons Casp8^*{:}BAR}$$
$$\mathrm{Casp3^* + IAP \rightleftharpoons Casp3^*{:}IAP}$$

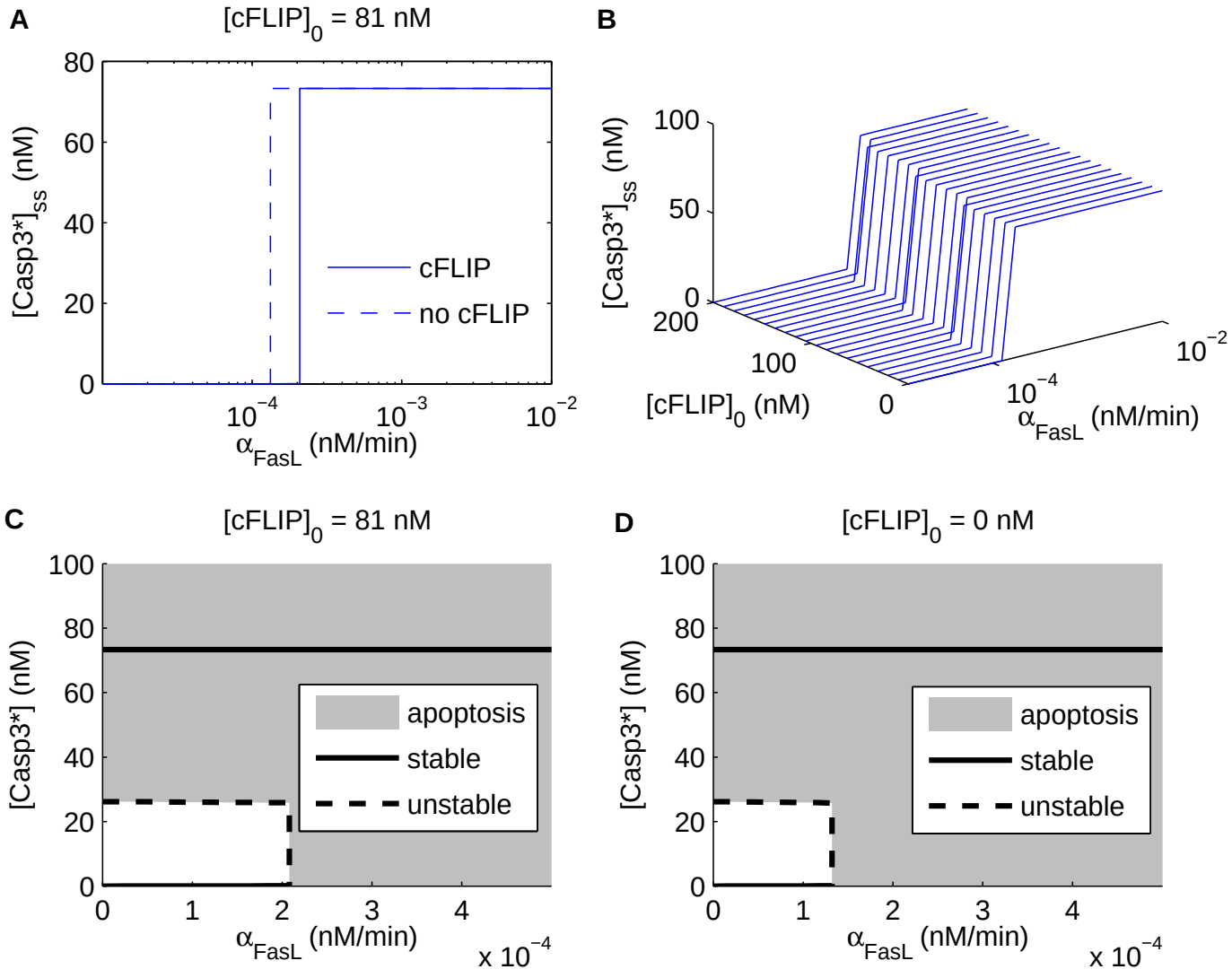
DISC model (3,3,3)



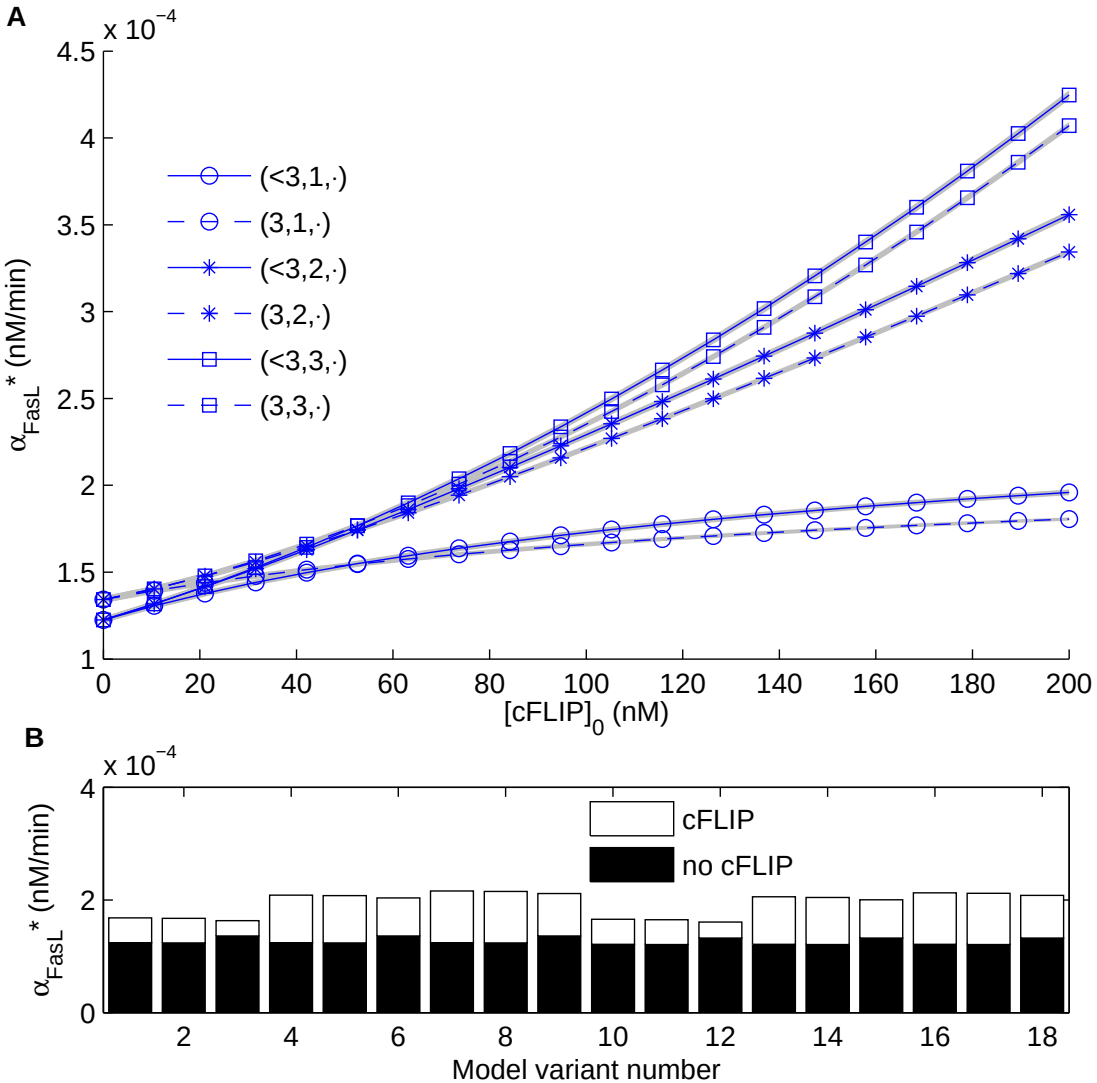
Comparison of DISC models



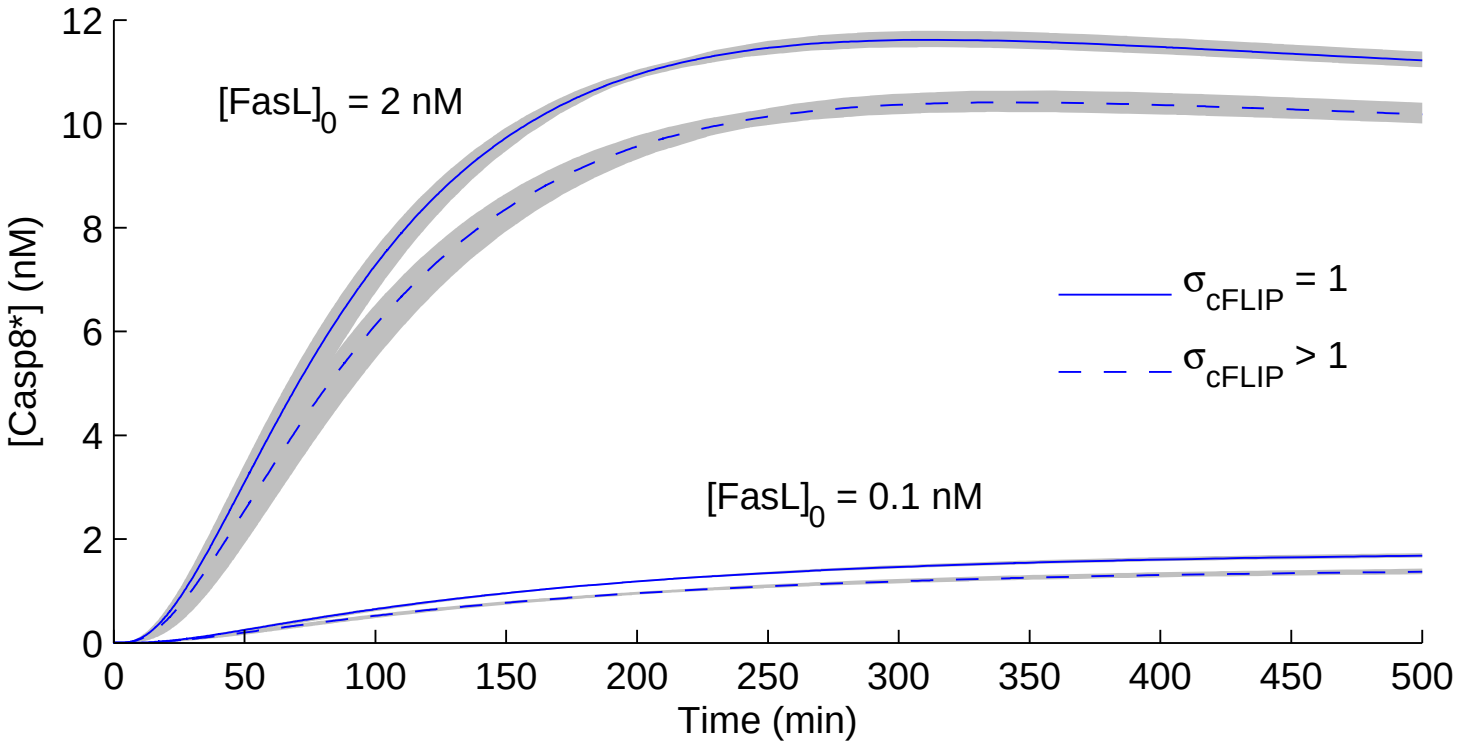
Coupled extrinsic caspase model (3,3,3)



Apoptotic threshold



DISC model time courses



Robustness with FasL

β: minimum fractional inhibitor reduction for apoptosis

- $[\mathrm{IAP}]_0 \mapsto (1-\beta)\,[\mathrm{IAP}]_0$ and $[\mathrm{BAR}]_0 \mapsto (1-\beta)\,[\mathrm{BAR}]_0$
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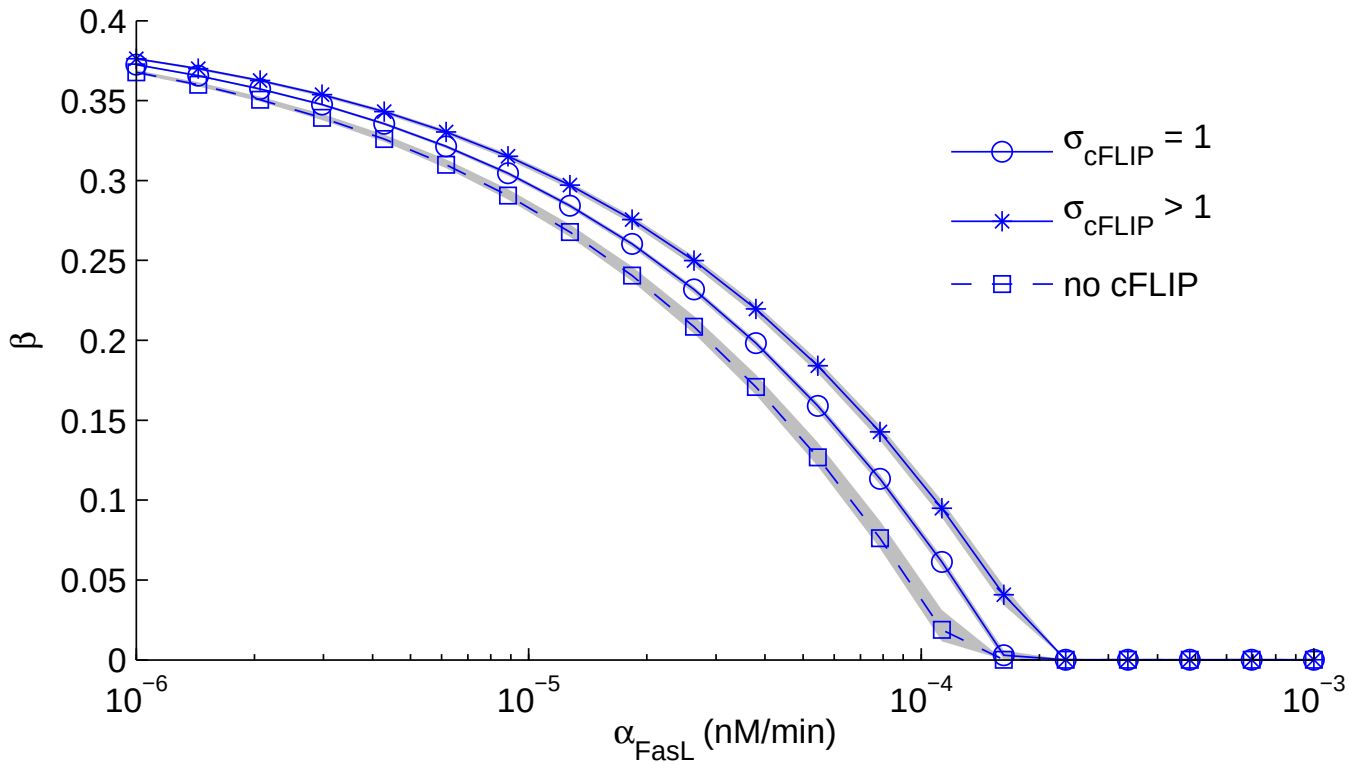
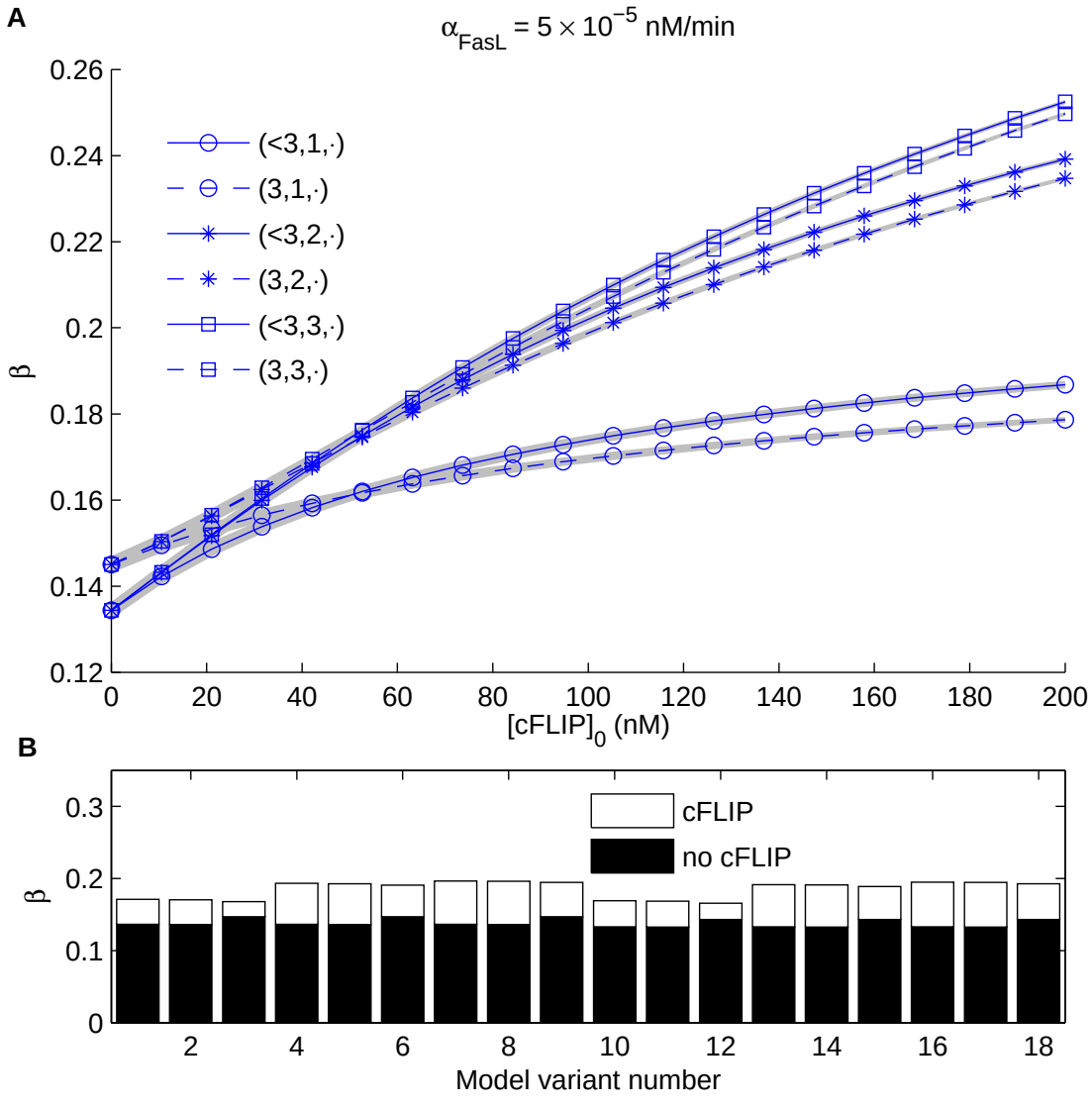


Robustness with cFLIP



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But the only truly significant result is bistability; the rest is just minor details if we're interested in bigger questions...

Ideas!

Use the DISC model as a component in a larger model to achieve a systems-level description that is complete and stable

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Any suggestions?

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