Prefrontal rhythms for cognitive control

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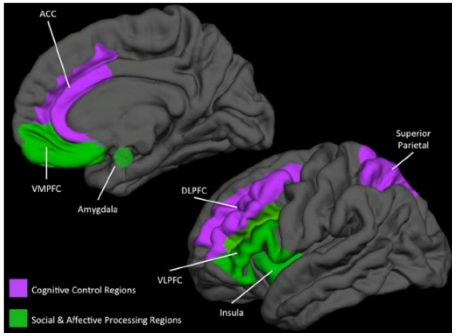
PhD Defense at Boston University
30-Mar-2017

Approach

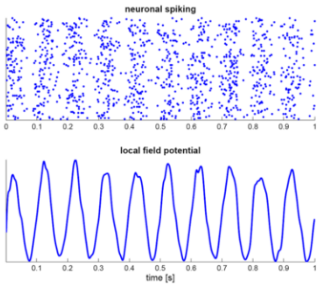
<u>Overarching goal</u>: Understand how frontal cortical network oscillations contribute to cognition.

<u>Cognitive processes</u>:
- Working memory
- Cognitive control

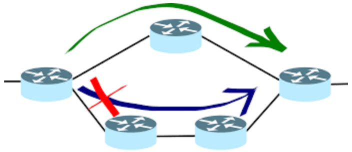


<u>Brain regions</u>:
- LPFC
- ACC

<u>Network dynamics</u>:
- Oscillations
- Resonance



<u>Neural functions</u>:
- Gating/routing
- Monitoring



<u>Approach</u>:
- **Build models constrained by anatomy and physiology of relevant brain circuits.**
- **Use computational modeling to study the functional implications of network dynamics observed during cognitive tasks.**

Outline

1. Background
   1. **DynaSim**: a modeling tool
   2. Cognitive processes and related brain regions/dynamics
   3. Neural dynamics (oscillations and resonance)

2. Prefrontal rhythms for cognitive control: **pathway selection**
   (gating and rule-based S→R mapping)

3. Prefrontal rhythm control (rule selection)

4. ACC heterogeneity for **combinatorial processing**
   (evaluation for regulating cognitive control)

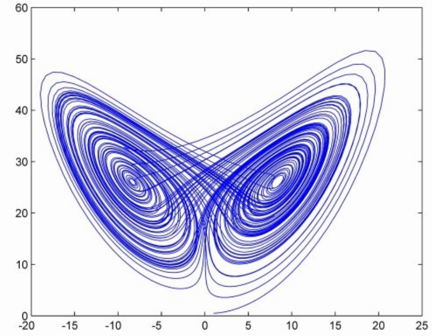
Background

DynaSim – MATLAB Toolbox for Modeling and Simulation

www.GitHub.com/DynaSim

Example: Lorenz equations:

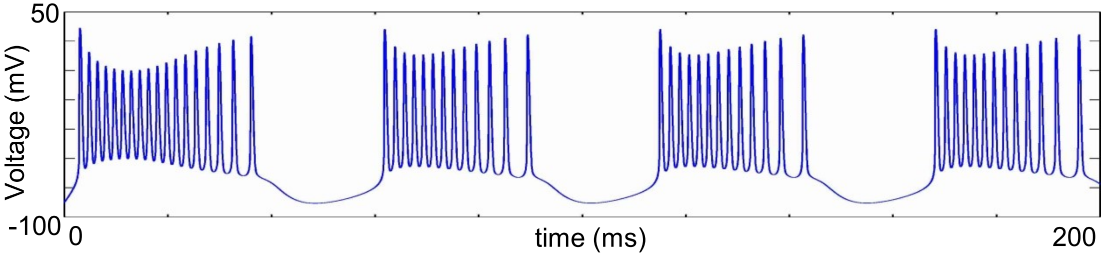
```
eqns={
  's=10; r=27; b=2.666';
  'dx/dt=s*(y-x)';
  'dy/dt=r*x-y-x*z';
  'dz/dt=-b*z+x*y';
};
data=SimulateModel(eqns,'tspan',[0 100],'ic',[1 2 .5]);
figure; plot(data.pop1_x,data.pop1_z)
```



Pass equations directly to SimulateModel.

Example: Hodgkin-Huxley-type bursting neuron:

```
eqns='dv/dt=5+@current; {iNaF, iKDR, iM}; v(0)=-70';
data=SimulateModel(eqns,’time_limits',[0 200]);
figure; plot(data.time,data.pop1_v))
```

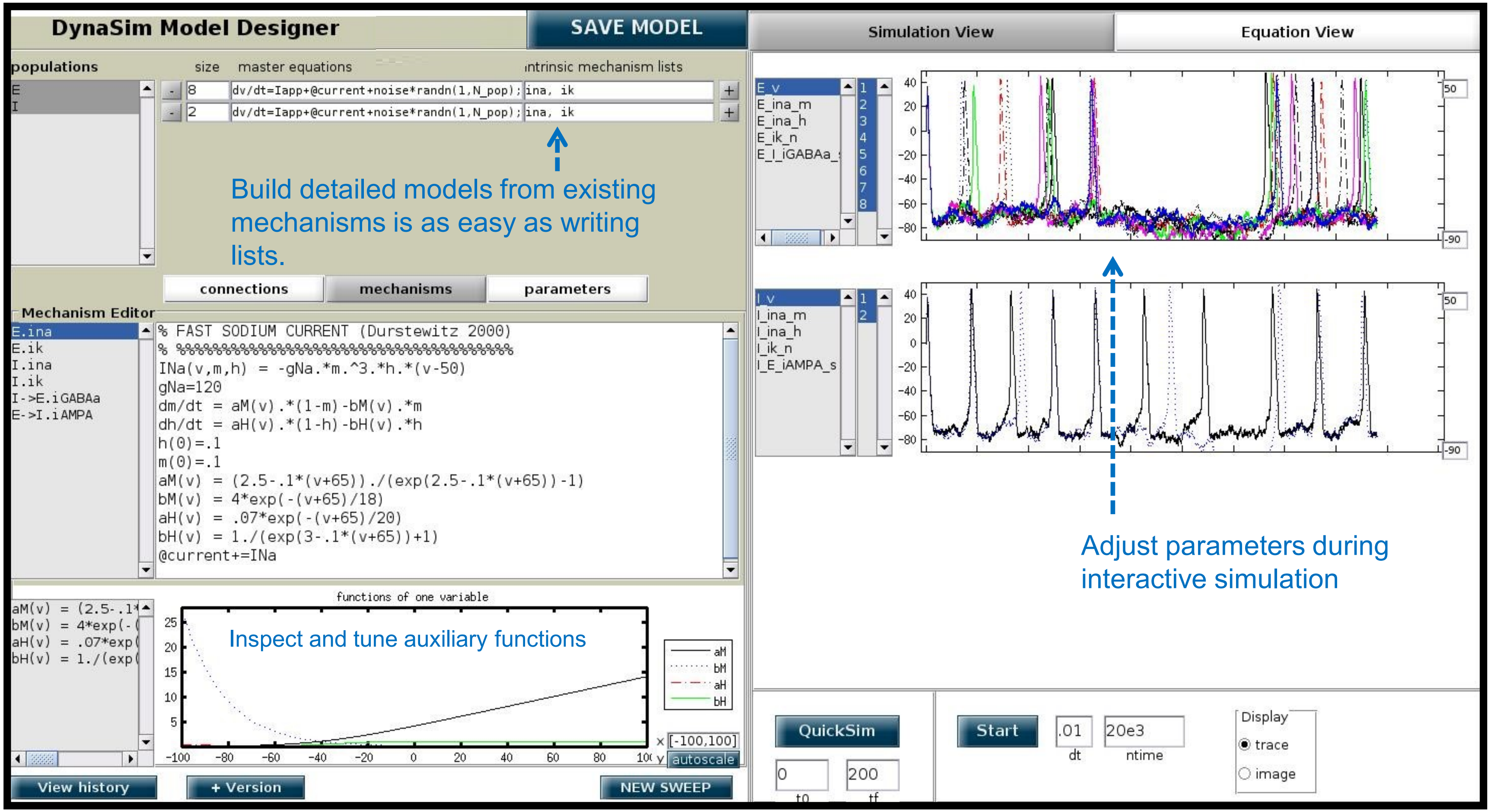


Larger models can easily build on existing model objects (e.g., “mechanisms”).

DynaSim – Graphical Interface for Modeling and Simulation

www.GitHub.com/DynaSim

View full model equations and dynamics during interactive model building



populations	size	master equations	intrinsic mechanism lists
E	8	dv/dt=Iapp+@current+noise*randn(1,N_pop);	ina, ik
I	2	dv/dt=Iapp+@current+noise*randn(1,N_pop);	ina, ik

Build detailed models from existing mechanisms is as easy as writing lists.

Mechanism Editor:

- E.ina
- E.ik
- I.ina
- I.ik
- I->E.iGABAa
- E->I.iAMPA

```
% FAST SODIUM CURRENT (Durstewitz 2000)
% %%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
INa(v,m,h) = -gNa.*m.^3.*h.*(v-50)
gNa=120
dm/dt = aM(v).*(1-m)-bM(v).*m
dh/dt = aH(v).*(1-h)-bH(v).*h
h(0)=.1
m(0)=.1
aM(v) = (2.5-.1*(v+65))./(exp(2.5-.1*(v+65))-1)
bM(v) = 4*exp(-(v+65)/18)
aH(v) = .07*exp(-(v+65)/20)
bH(v) = 1./(exp(3-.1*(v+65))+1)
@current+=INa
```

```
aM(v) = (2.5-.1*
bM(v) = 4*exp(-(
aH(v) = .07*exp(
bH(v) = 1./(exp(
```

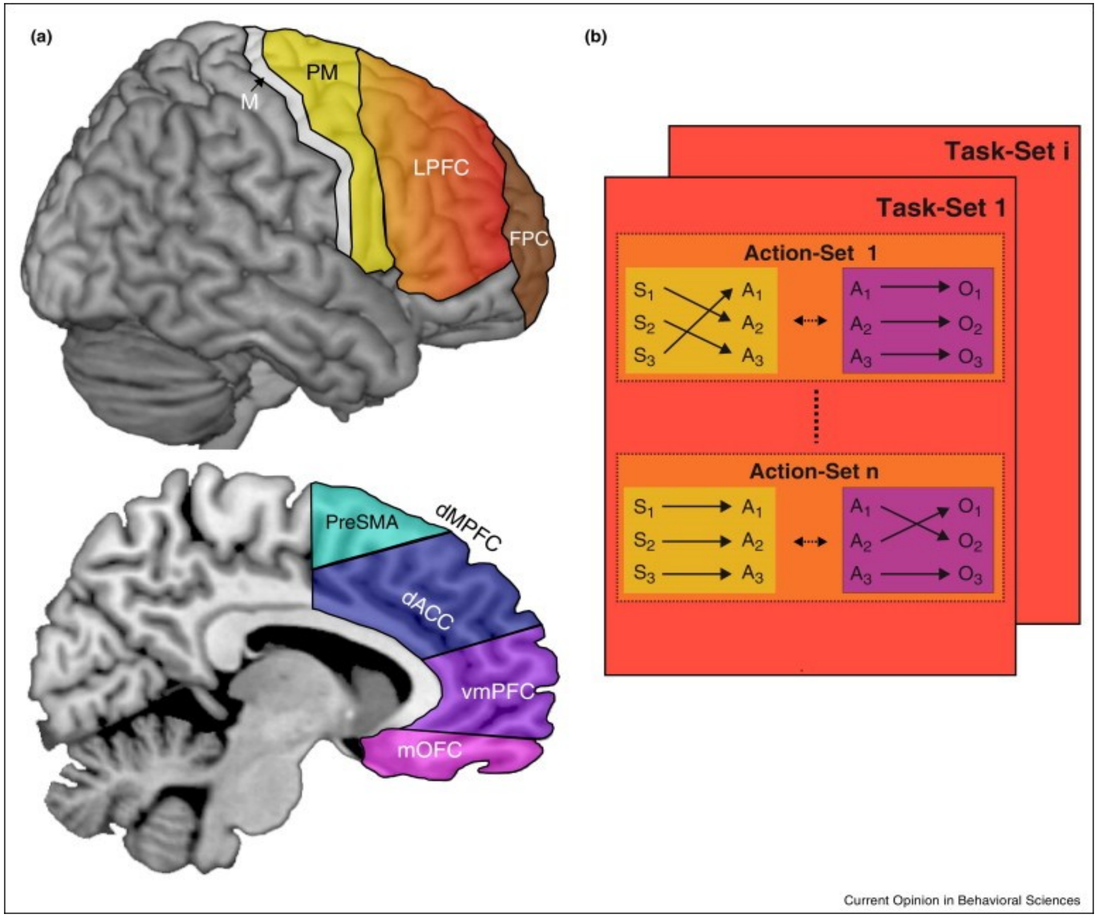
Inspect and tune auxiliary functions

x [-100,100]

Adjust parameters during interactive simulation

t0: 0
tf: 200
dt: .01
ntime: 20e3
Display: ● trace ○ image

Rule-Based Cognitive Control



- **Cognitive control**: process of manipulating task-relevant info while ignoring distractors.
- **DLPFC** exerts cognitive control by **biasing** info flows in service of goals (**pathway selection**). It codes context-dependent "**rules**" (i.e., abstract sets of IF/THEN statements that direct input-output mappings), indicating what is relevant and how to manipulate it.
- **ACC** **monitors** diverse signals (e.g., errors, conflicts, reward) to perform a cost/benefit analysis for regulating cognitive control (e.g., **updating** rules).

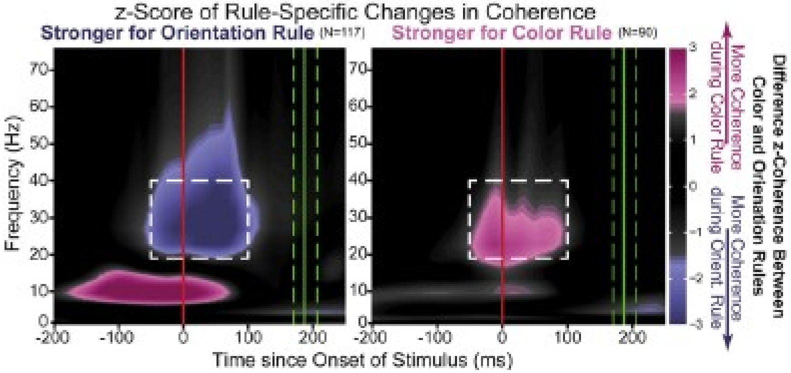
I will focus on how network rhythms may contribute to rule-based cognitive control through their effects on dynamics in ACC and DLPFC (monitoring, updating, biasing).

Domenech, Koechlin. Current opinion in behavioral sciences 2015.

Prefrontal Rhythms: Experimental Motivation

PFC Rhythms in Cognitive Tasks

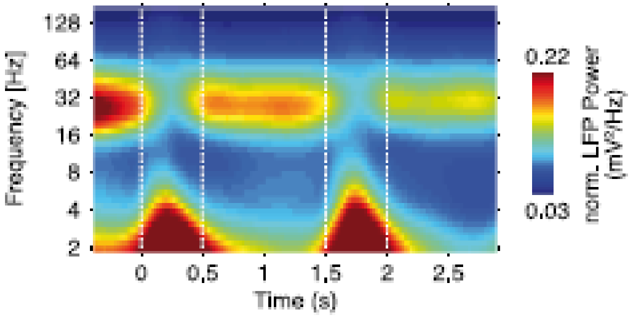
Task with rule switching



Active rule-selective ensembles are coherent with a beta2 oscillation

Buschman, Denovellis, Diogo, Bullock, Miller. Neuron 2012.

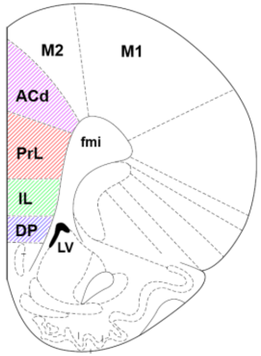
Two-item short term memory task



32Hz network rhythm during delay

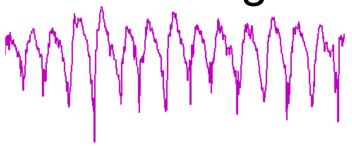
Siegel, Warden, Miller, PNAS 2009

PFC Wants to Oscillate (in vitro)

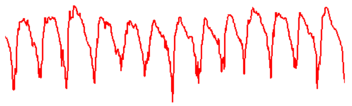


Carbachol/Kainate

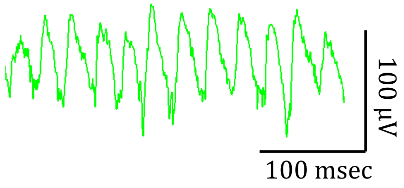
Anterior cingulate

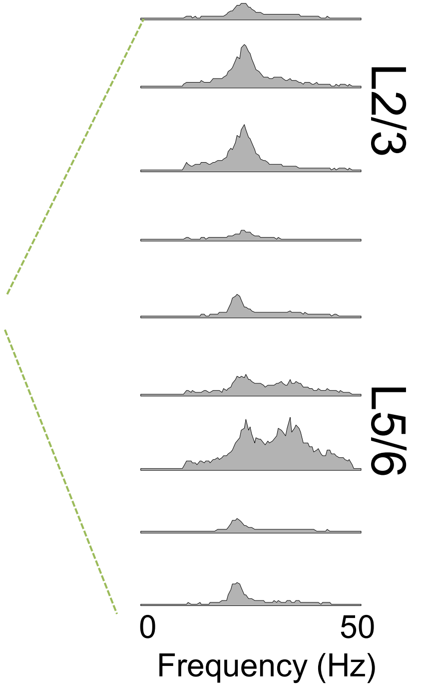


Prelimbic cortex



Infralimbic cortex





LeBeau (unpublished data)

Network freq. depends on:

- **cortical region**
- **cortical layer**
- **agonist/antagonist**

Results:

From Dynamics to Function

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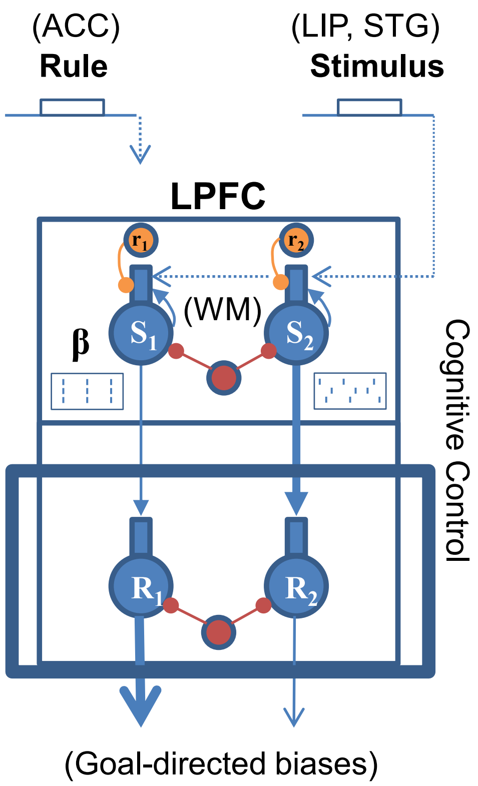
LPFC Cognitive Rhythms

Question: How do rhythms contribute to rule-based pathway selection?

(conceptual model)



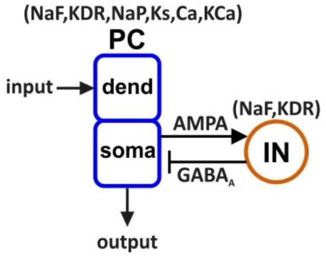
● CB+ LTS INs
● PV+ FS INs
● Homogeneous PCs

(computational model)

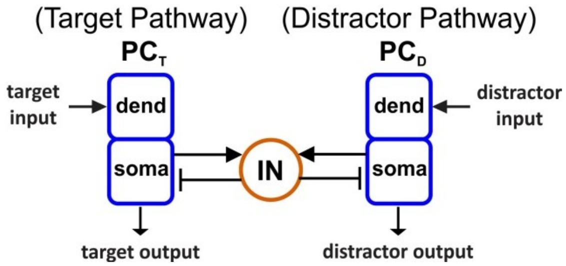
We will see:

- **There is beta resonance in deep layers, even though FS cells can support gamma resonance.**
- **Pathways with resonant inputs can be selected over stronger pathways with less resonant inputs.**

PFC network model



PFC competition model



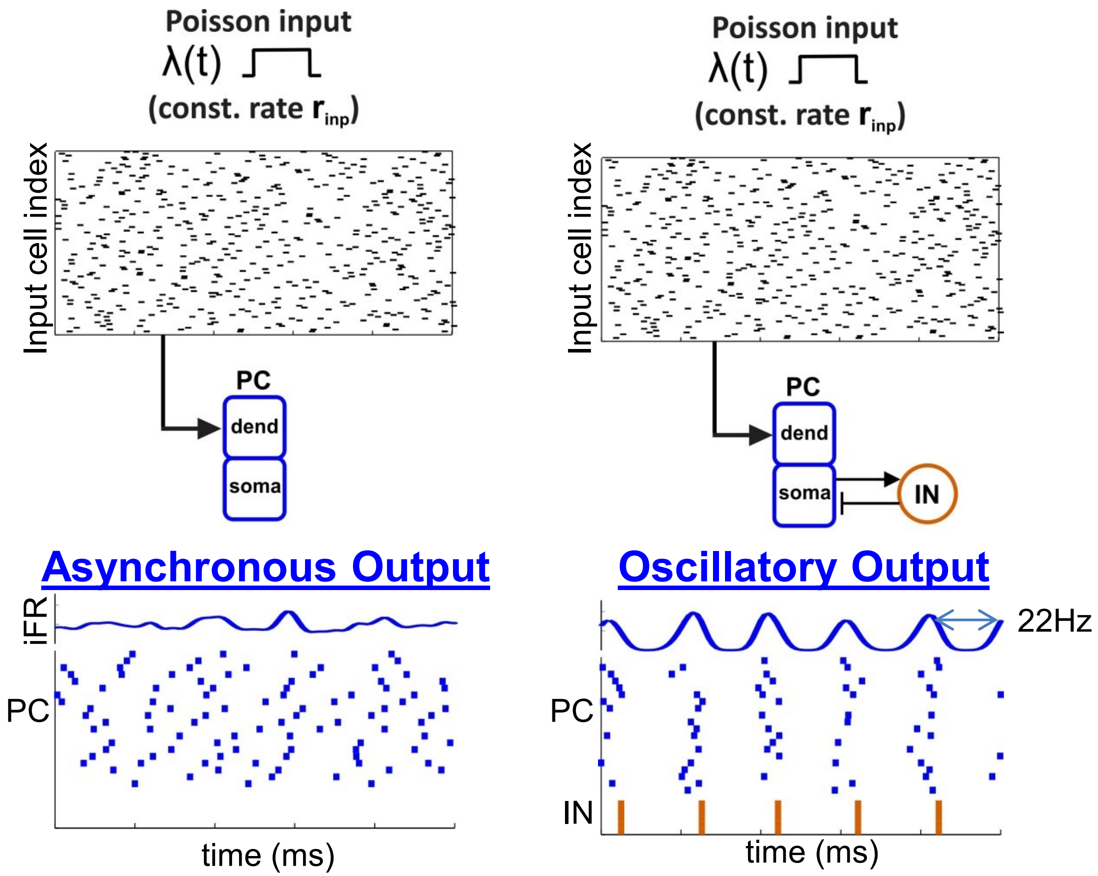
Biophysical PFC L5 cell model:

$$C_m \frac{dV_{PY}}{dt} = I_{ext}(t) - I_{Na} - I_K - I_{NaP} - I_{Ca} - I_{KCa} - I_M - I_h - I_{leak}$$

Durstewitz, Daniel, and Jeremy K. Seamans. *Neural Networks* 15.4 (2002): 561-572

Feedback Inhibition Produces Natural Oscillation

Asynchronous Input: Unmodulated Poisson λ(t)



"distractor response"

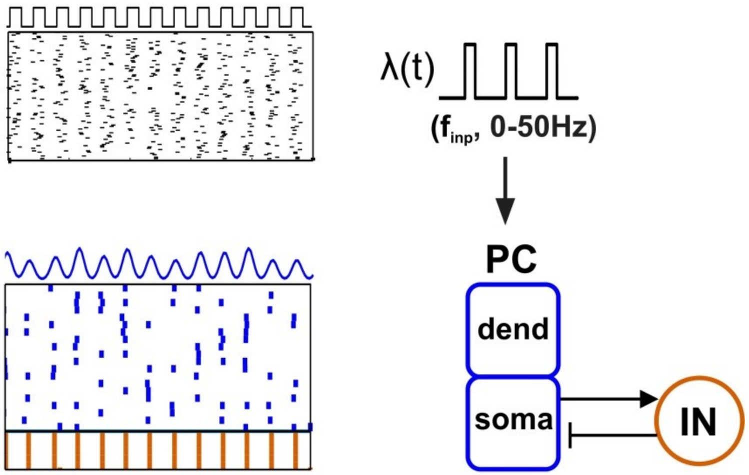
- **Strong feedback inhibition turns asynchronous input into an oscillatory output at the level of the population.**
  (not necessarily visible in single cells)
- **Population frequency = the frequency of population oscillation.**
- **Natural frequency = population frequency in response to an asynchronous input.**

PC/IN Network Response is:

- **Inhibition-paced: pop frequency decreases with inhibition duration.**
- **Variable-freq oscillator: pop frequency increases with input strength.**

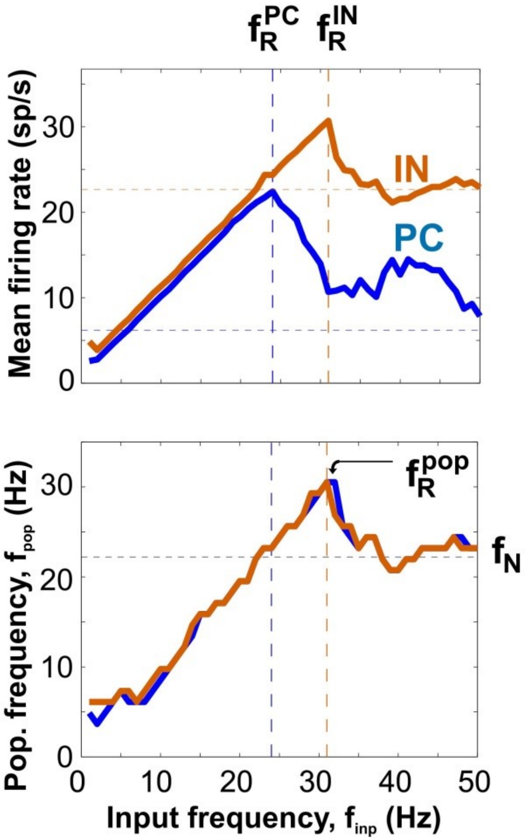
Oscillatory Input Produces Greater Output

Oscillatory Input: Periodically modulated Poisson λ(t)



"target response"

Two types of output



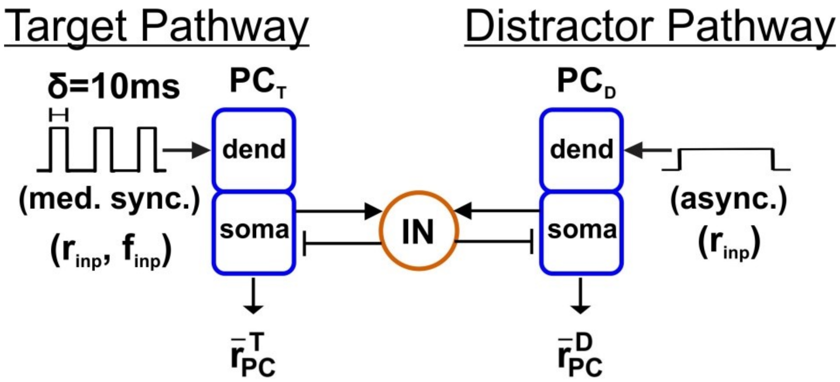
Resonant frequency: Input freq. that maximizes output.

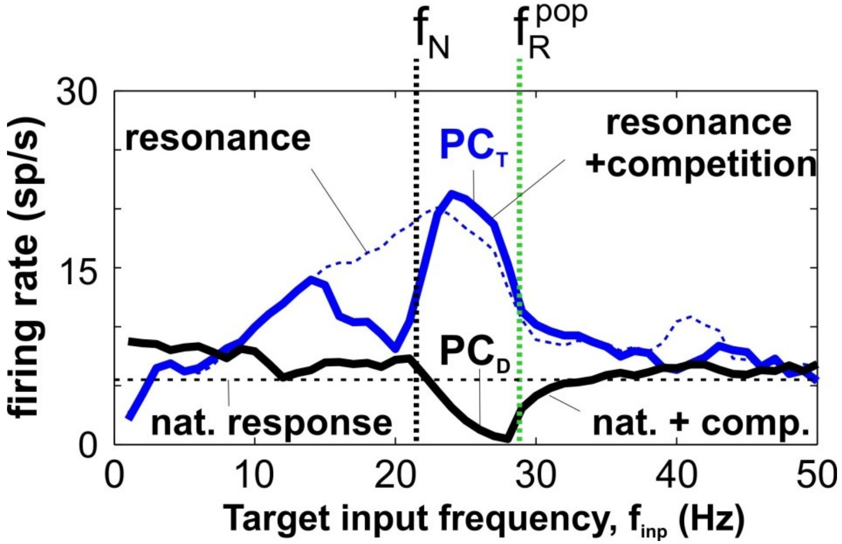
- **IN cells exhibit higher FR resonant frequency**
- **Max. pop. frequency = FR resonant freq (IN)**
- **Despite cell differences, PC and IN pops exhibit the same rhythmicity**

- **Resonant frequencies increase with input strength**
- **Max pop. frequency always exceeds natural frequency**

(i.e., it is always possible for the target to oscillate faster than distractor)

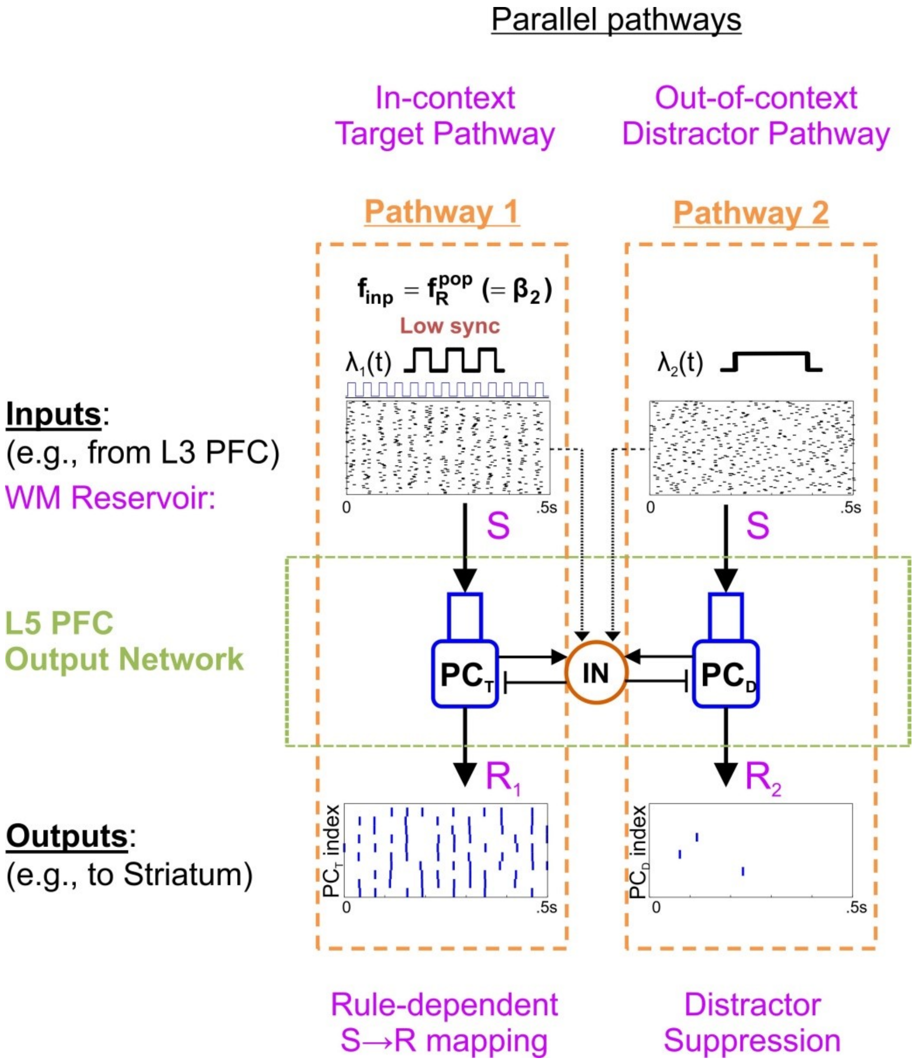
Biased Competition: Resonant Target Suppresses Asynchronous Distractors





- Resonant inputs gate response to competing asynchronous activity.
- Suppression occurs when <u>target pop. freq. > natural freq.</u> of distractor.
    - Per cycle, target PCs drive INs before distractor PCs reach thresh.
- Stronger async. distractors can be suppressed by more sync. targets.
- <u>High sync. target can produce more spike output than 70% stronger async. distractor.</u>
- Suppression can be amplified for winner-take-all selection by recurrent excitation within output pops (i.e., learning across trials).

Cognitively-Relevant Example of Distrator Suppression (Gating) with Rhythm-Mediated Biased Competition



Parallel pathways

In-context Target Pathway

Out-of-context Distractor Pathway

Pathway 1

Pathway 2

Inputs: (e.g., from L3 PFC)

WM Reservoir:

L5 PFC Output Network

Outputs: (e.g., to Striatum)

Rule-dependent S→R mapping

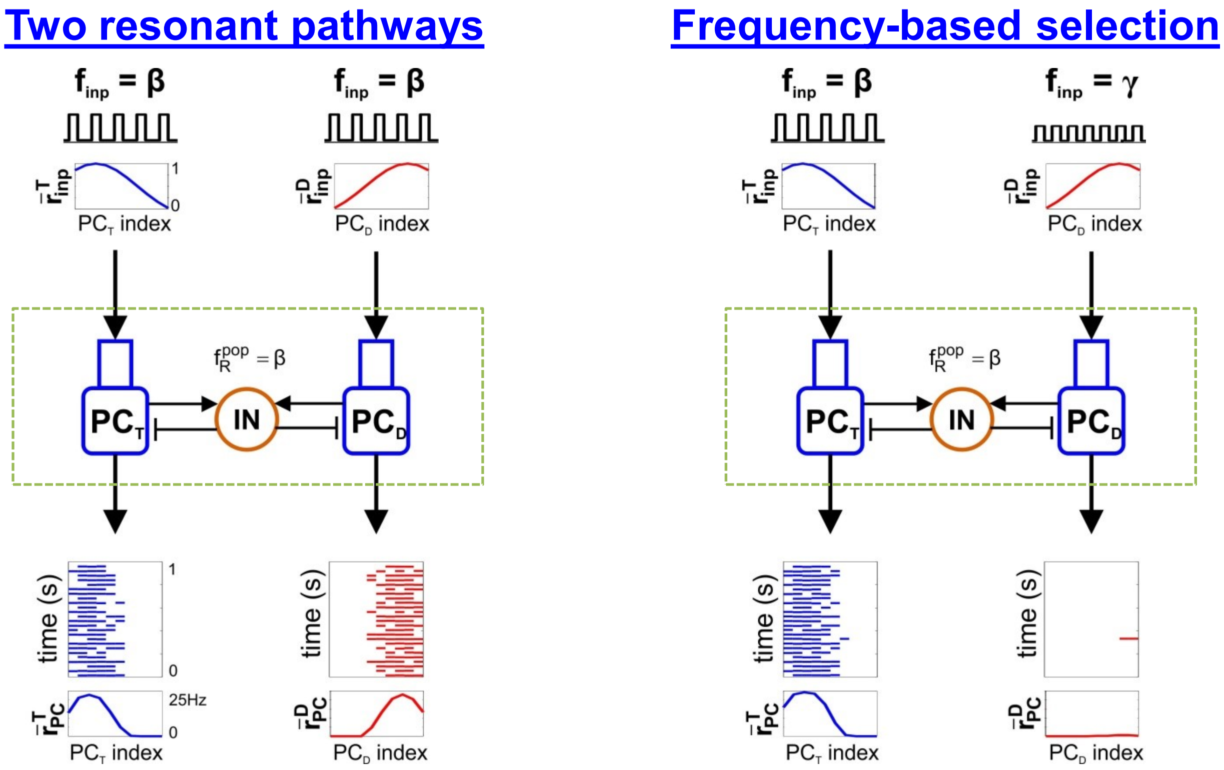
Distractor Suppression

- Pathway selection depends on matching input frequency to output resonant frequency.

- LPFC L2/3 rule-related beta-rhythmic assembly successfully drives L5 target.

- LPFC L2/3 asynchronous “memory” is retained in superficial layers without driving L5 target (i.e., without being transmitted to downstream targets).

Resonant Bias Can Gate Rate-Coded Signals Among Parallel Pathways

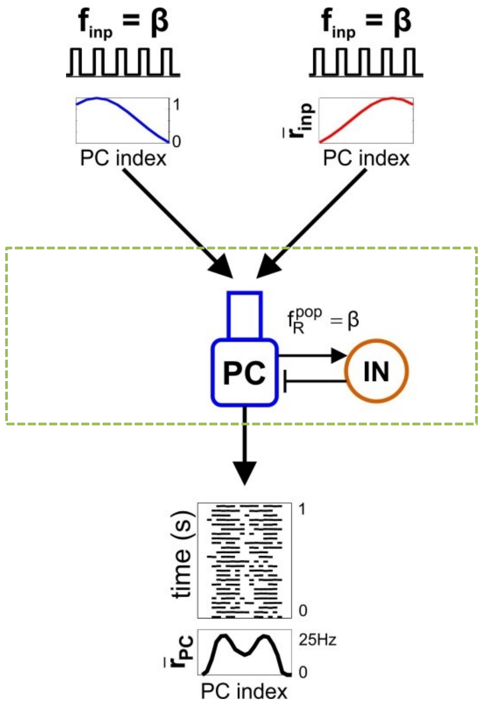

Two resonant pathways

Frequency-based selection

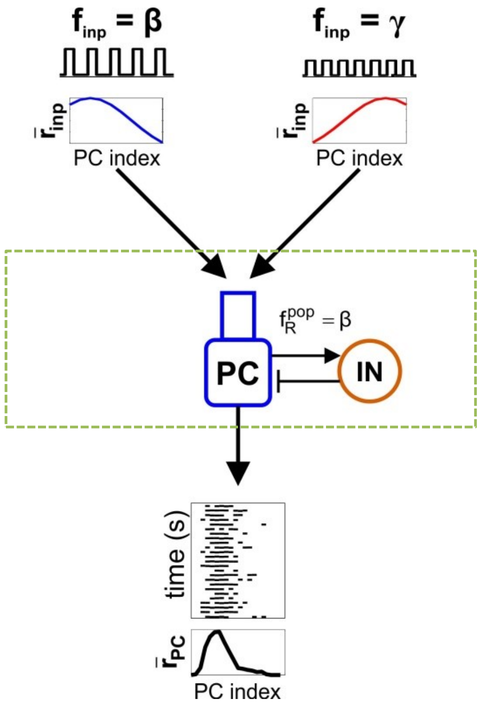
- **Input pattern of firing rates is reflected across the output populations.**
- **A resonant input phase locks with INs and suppresses response to less resonant signal.**
- **A more coherent input can suppress response to less coherent signal.**

Resonant Bias Can Gate Rate-Coded Signals Among Convergent Pathways

Two resonant pathways

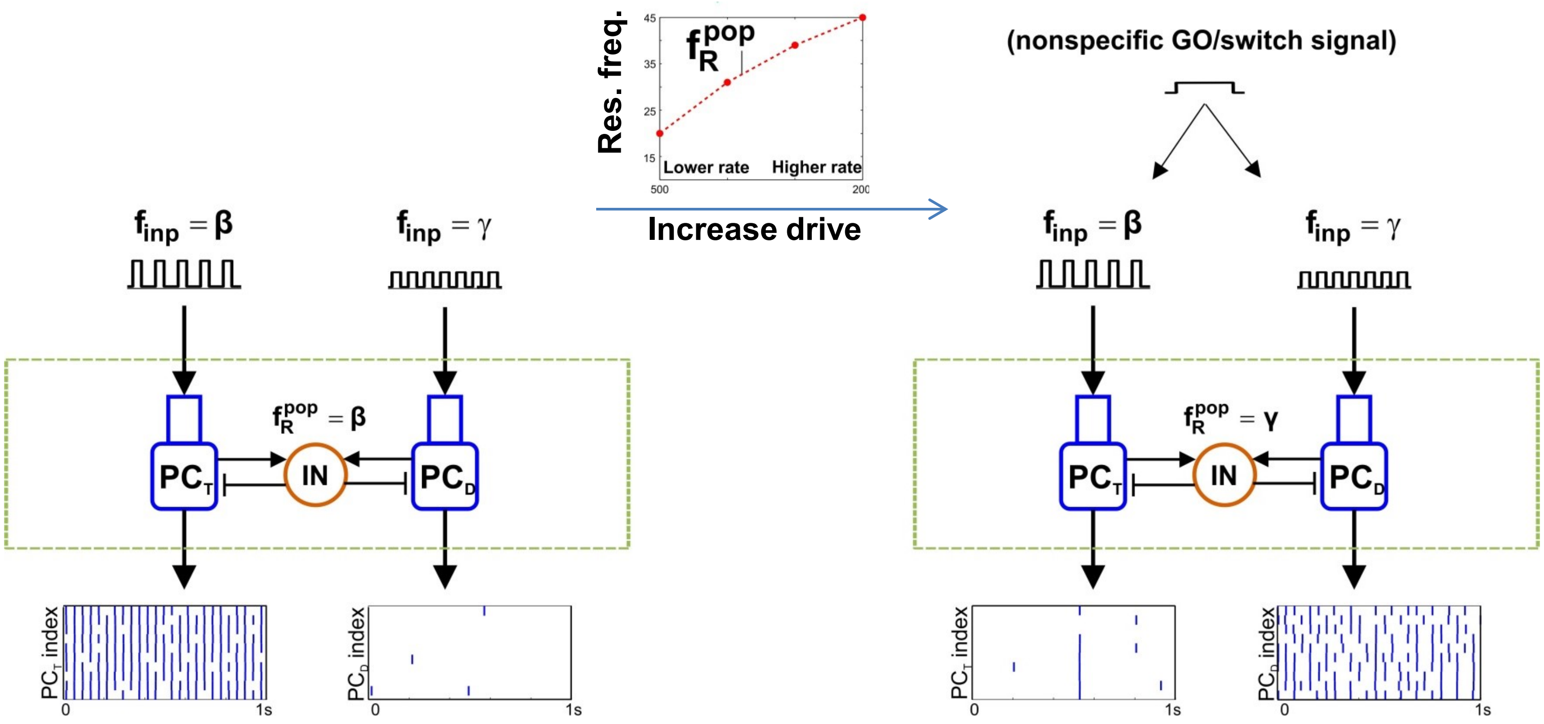


Frequency-based selection



- **Firing rate pattern of multiple inputs can be reflected across a single output population.**
- **A resonant input phase locks with INs and blocks response to less resonant signal.**

Nonspecific Input Selects Beta vs. Gamma by Setting Target Resonant Frequency



- "GO" → <u>output layer</u>: dominant pathway switches w/ target res. freq.
- "GO" → <u>input layer</u> (variable-freq. oscillators): source freq. increases w/ target res. freq., and the same pathway remains dominant.

Summary / Discussion (so far): Connection to Cognitive Processes

DLPFC:

- Can control which input-output mappings are engaged by controlling participation in a resonant oscillation.

- Separation of representations in superficial and deep layers allows memory in superficial layers to be distinct from output (beta)

- Can flexibly tune resonant frequency via input rate and tune degree of response through synchrony of the input.

Implication: Non-specific GO signal can lead to specific outcome

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3. **Prefrontal rhythm control (rule selection)**

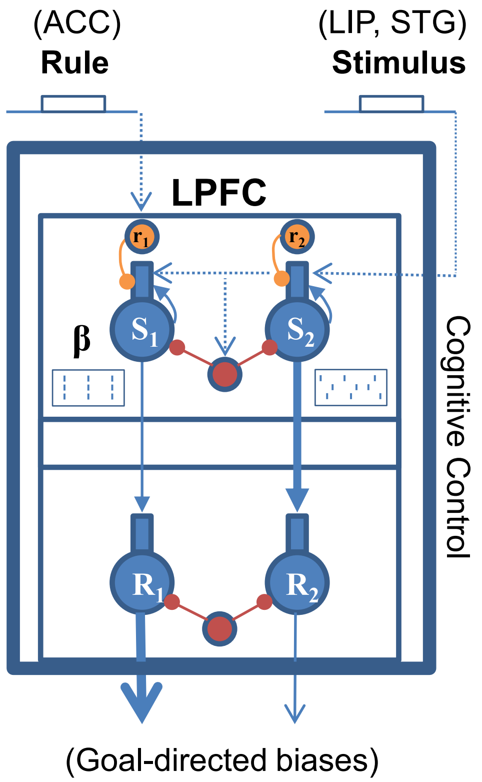
4. ACC heterogeneity for combinatorial processing (evaluation for regulating cognitive control)

LPFC Cognitive Rhythms: Rule Selection

Question: What controls rule-specific beta-rhythmicity?

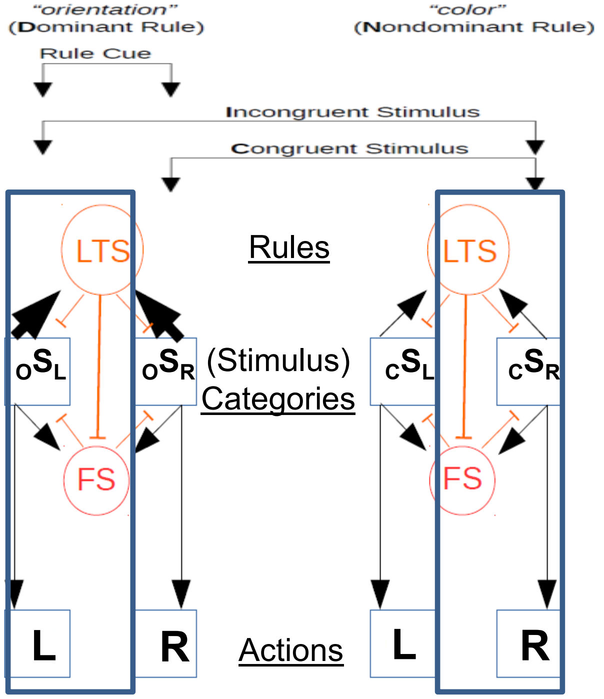
H: Context (rule) is represented by activation of subset of CB+ LTS interneurons. Leads to resonant beta frequency activity in superficial layers.

(conceptual model)



● CB+ LTS INs
● PV+ FS INs
● Homogeneous PCs

Rule-based task model



Key differences between IN types

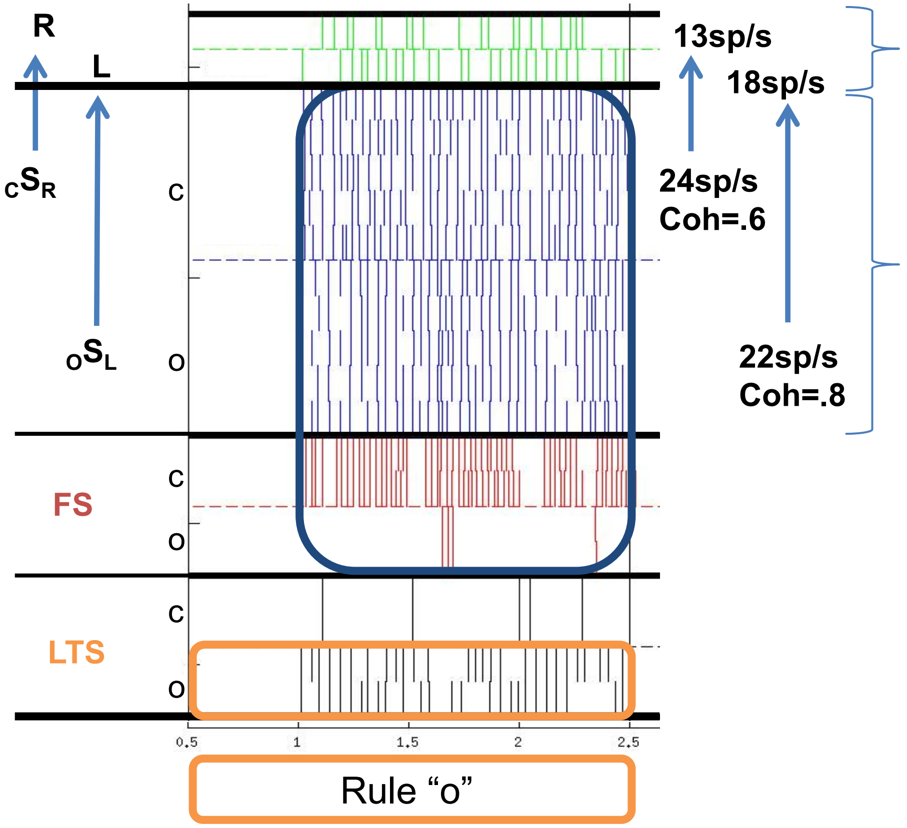
1. Inhibition strength: LTS > FS
   (LTS → more coherent PCs)
2. Inhibition duration: LTS > FS
   (LTS → beta rhythmic PCs)

(beta res. in deep layers)

Consider: two trials with the same incongruent stimulus ($_O S_L$, $_C S_R$) and different contexts/rules ("o" vs "c").

(Incongruent stimulus: maps to different responses in different rules)

CB+ LTS Activity Selects Beta-Rhythmic Assembly, and thus Response Mapping Via Biased Competition

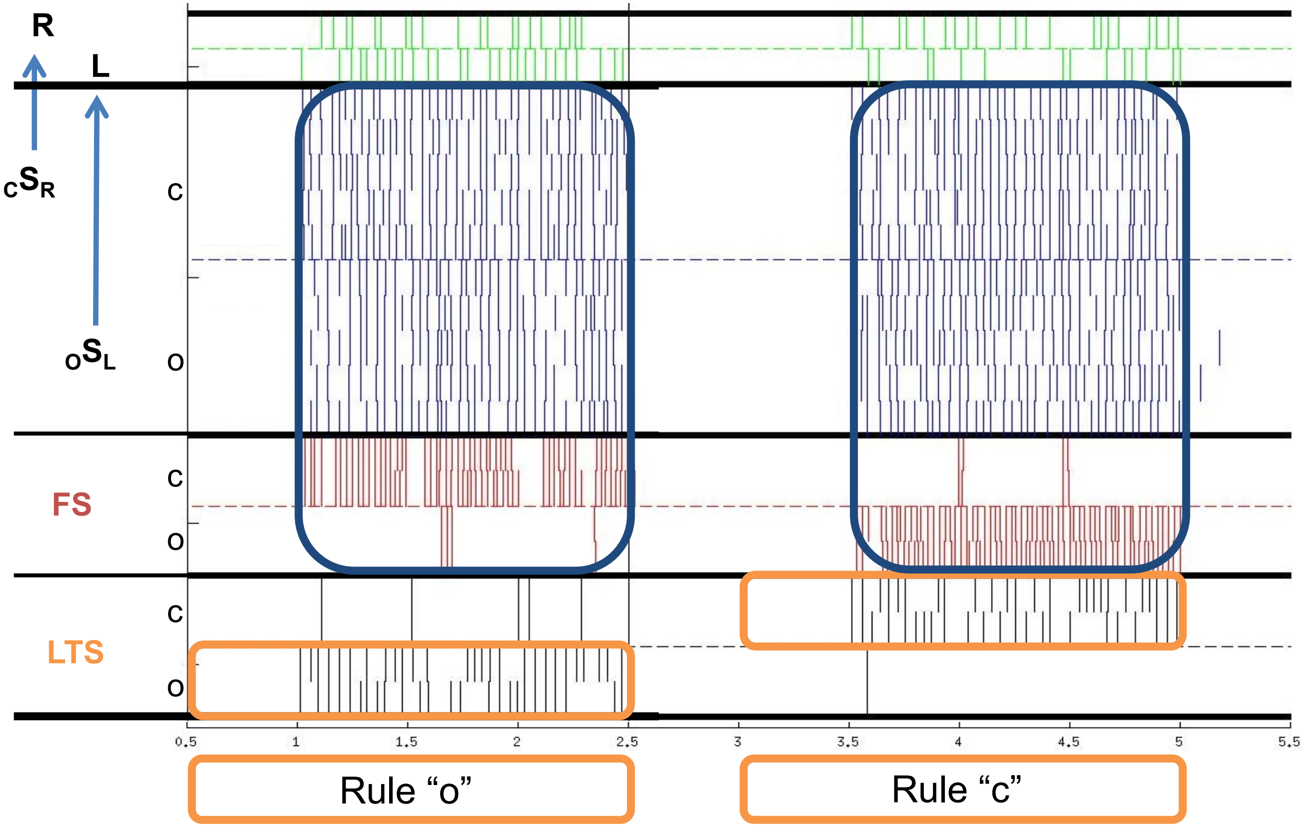


L > R

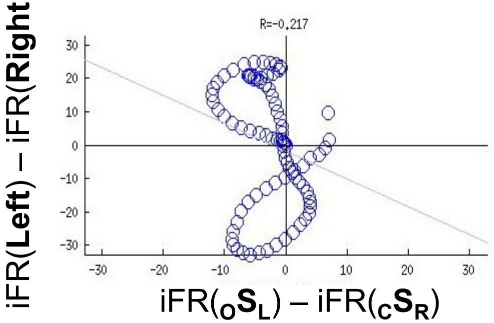
$_O S_L < {}_C S_R$

Driving LTS cells selects mapping inhibited by them (via resonant beta-rhythmic bias).

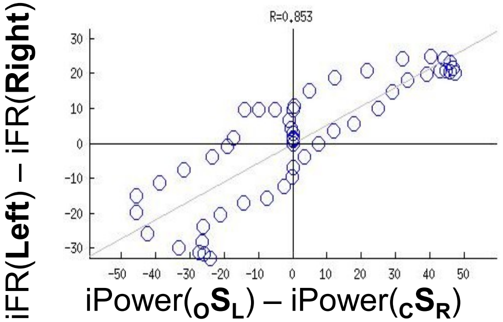
CB+ LTS Activity Selects Beta-Rhythmic Assembly, and thus Response Mapping Via Biased Competition



Rates do not predict output



Beta power predicts output



- The only change from one rule to the next is which LTS cells were driven.
- The output is predicted by LTS-dependent beta power, not input firing rates.

Conclusions for DLPFC

- **Context-sensitive LTS inhibition induces beta-rhythmicity** in coupled assemblies (collectively specifying a “rule”). Could be triggered by transient input from ACC.

- **Resonance-mediated bias for rule-dependent action**: the beta-rhythmic assembly produces greater spiking in its target relative to a higher spike rate non-rhythmic assembly.

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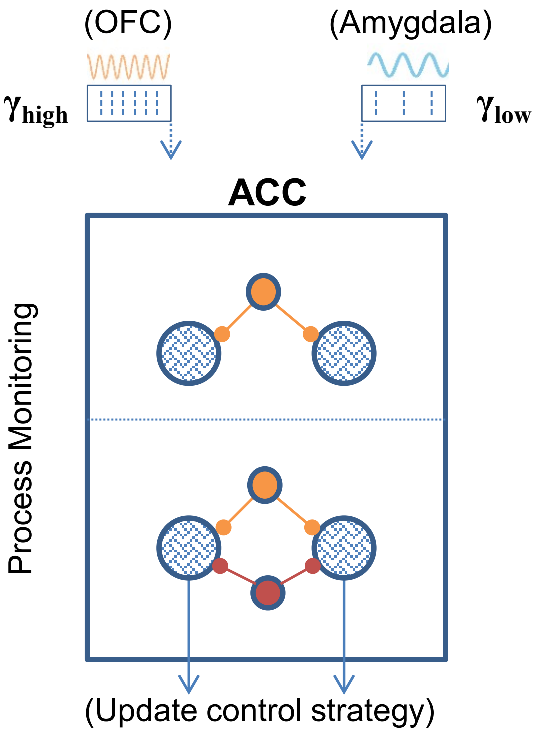
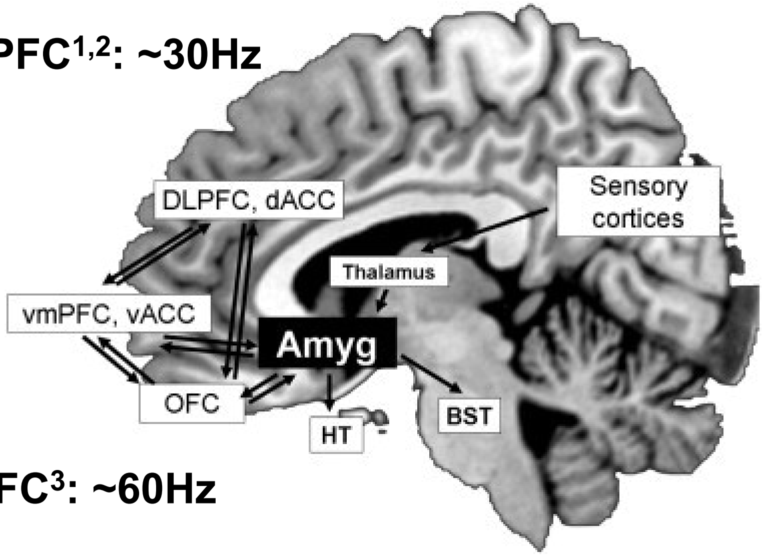
ACC Heterogeneity for Process Monitoring



● CB+ LTS INs
● PV+ FS INs
▨ Heterogeneous PCs

ACC receives inputs from many systems at different frequencies:

LPFC[1,2]: ~30Hz



OFC[3]: ~60Hz

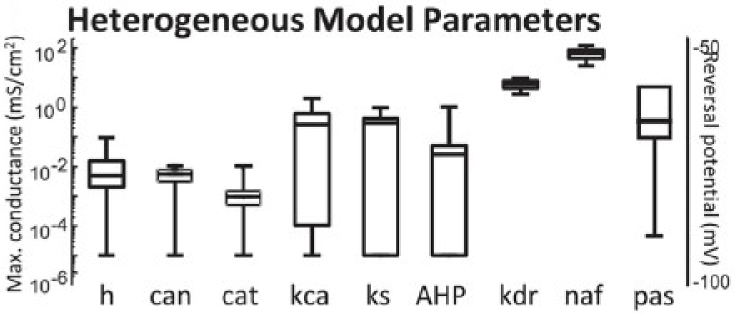
BLA: 35-45Hz **A2: 30-50Hz**

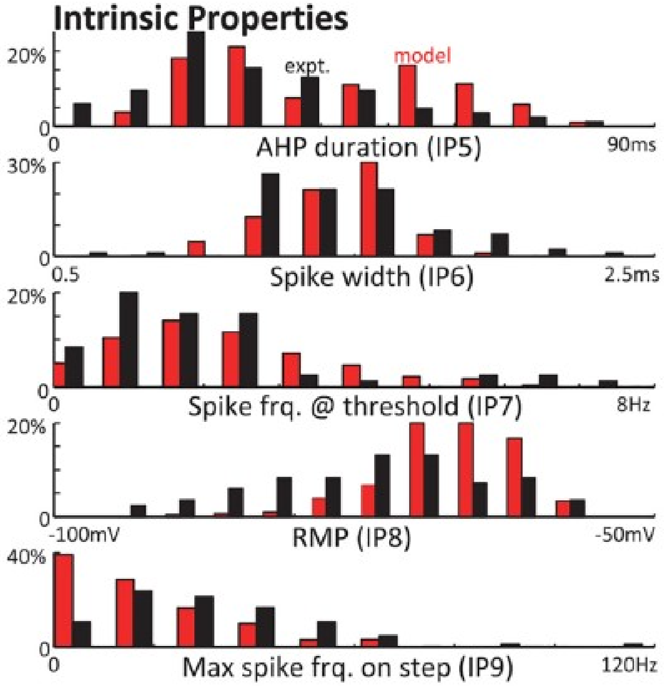
- **ACC monitors diverse signals (e.g., errors, conflicts, reward, uncertainty) for cost/benefit analysis to allocate resources for cognitive control.**
- **ACC outputs to PFC are implicated in updating rules for decision making.**

Question: How does ACC combine inputs at different frequencies?

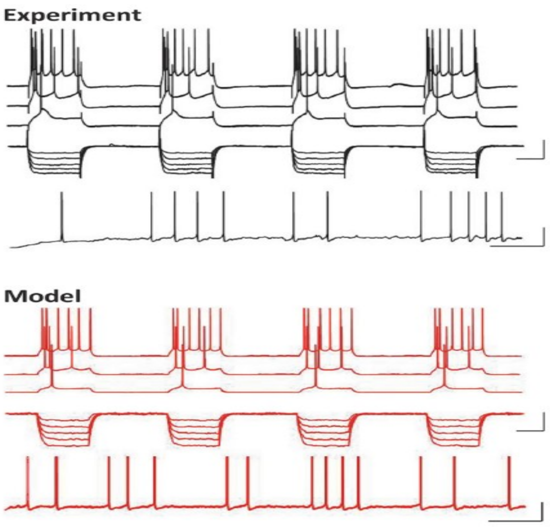
[1] Siegel, Warden, Miller. PNAS 2008. [2] Buschman, Denovellis, Diogo, Bullock, Miller. Neuron 2012. [3] Pennartz, van Wingerden, Vinck. *Annals of NY Acad of Sciences* 2011.

Heterogeneous Biophysical Models Reproduce the Range of Experimental Intrinsic Properties


Heterogeneous Model Parameters


Intrinsic Properties

- Recorded 61 (isolated) cells in ACC
- Modeled heterogeneity:
    - Simulated experimental protocol
    - Varied 9 parameters
    - Constrained 5 intrinsic properties
    - Tested >100,000 cell models
    - Found 2,810 viable models



ACC E-cells have intrinsic properties that are heterogeneous across the population.

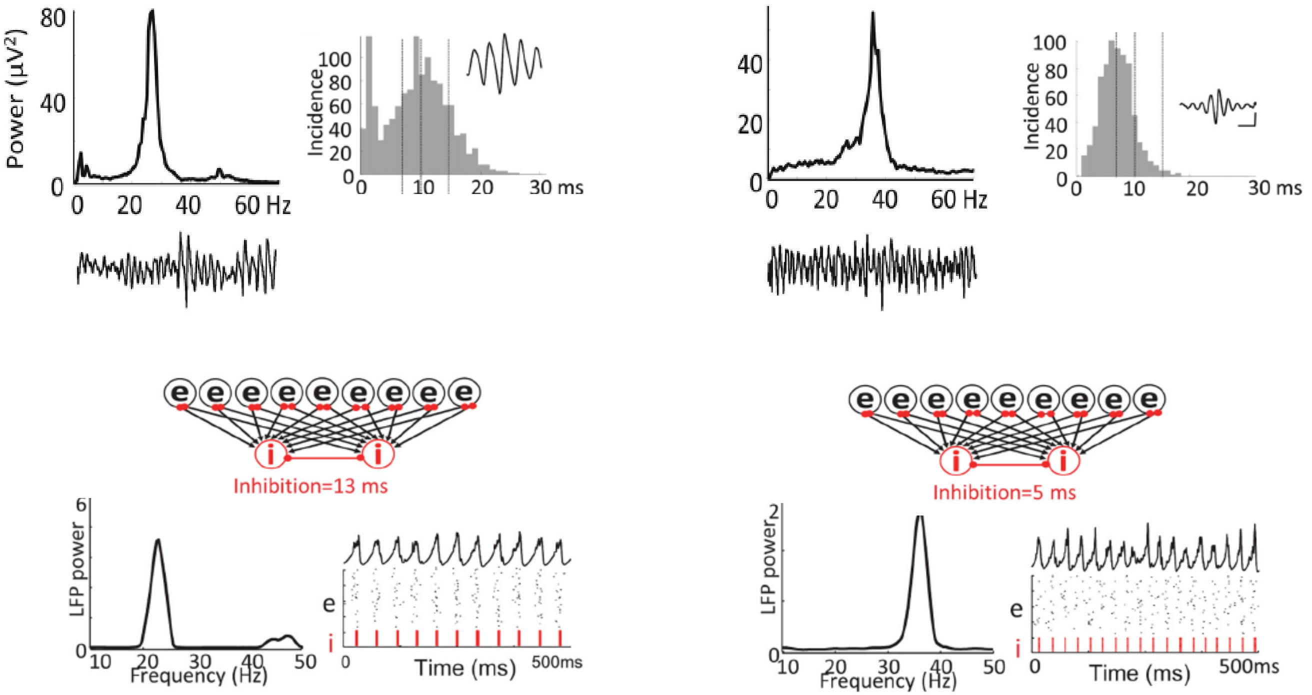
IPSPs Suggest Dual Inhibitory Inputs in ACC Cells During Gamma/Beta Network Oscillations

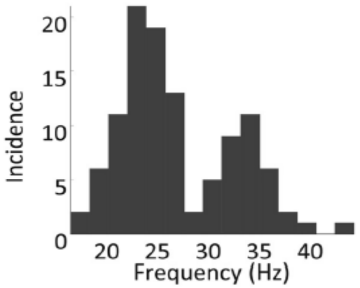
Beta rhythm **Gamma rhythm**

LFP **IPSP dur.** **LFP** **IPSP dur.**

Experiment

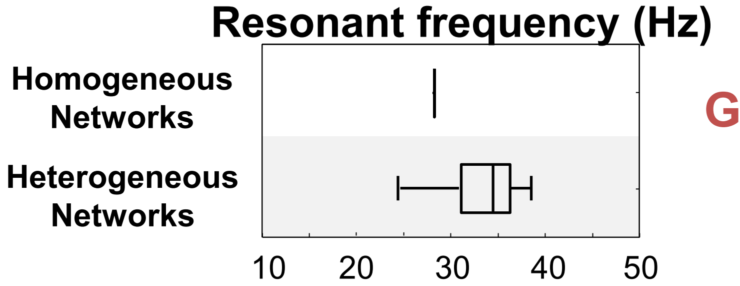
Model





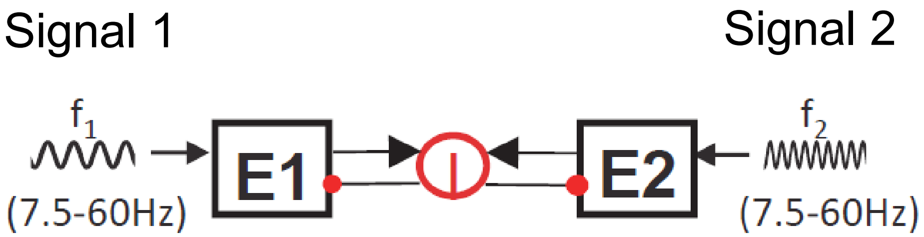
freqs across 109 ACC slices

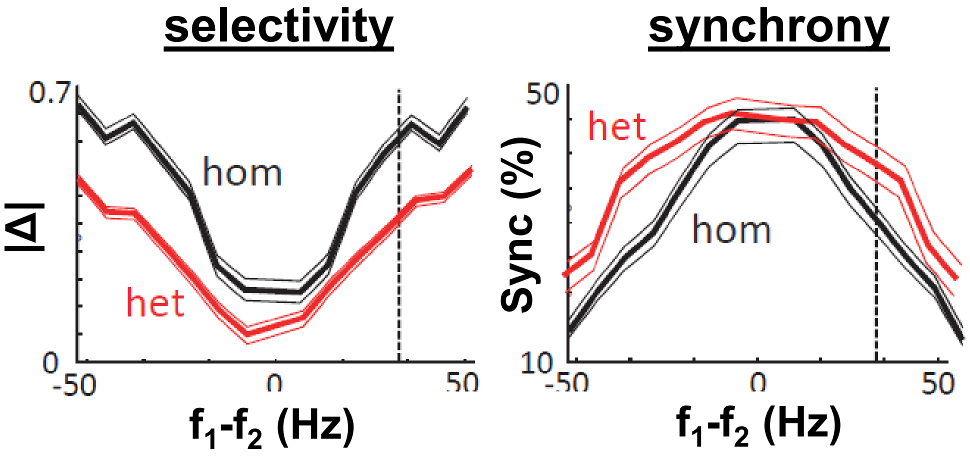
Heterogeneity expands the range of input frequencies that produce a (firing rate) resonant response.



Gamma IPSP

Heterogeneity of Target Decreases Selectivity and Increases Synchrony





- Networks with competing assemblies are less selective for input frequencies when E-cell assemblies are heterogeneous. Outputs are more synchronous.
- Heterogeneity has little effect when frequency differences are small.
- Similar result for assemblies driven by rhythmic vs. asynchronous activity.
- ACC heterogeneity may facilitate combinatorial evaluation for rule updating/task switching.

Δ = (fractional difference in firing rate)

Sync = (percent of 10ms bins with spiking in both assemblies)

Conclusions for ACC

ACC:

- Heterogeneity in target reduces competition and allows combination of signals associated with monitoring outcomes for updating cognitive control strategies (and possibly choice of rule)

- May provide signals that (directly or indirectly) update the "context" by activating selected CB+ cells in superficial DLPFC

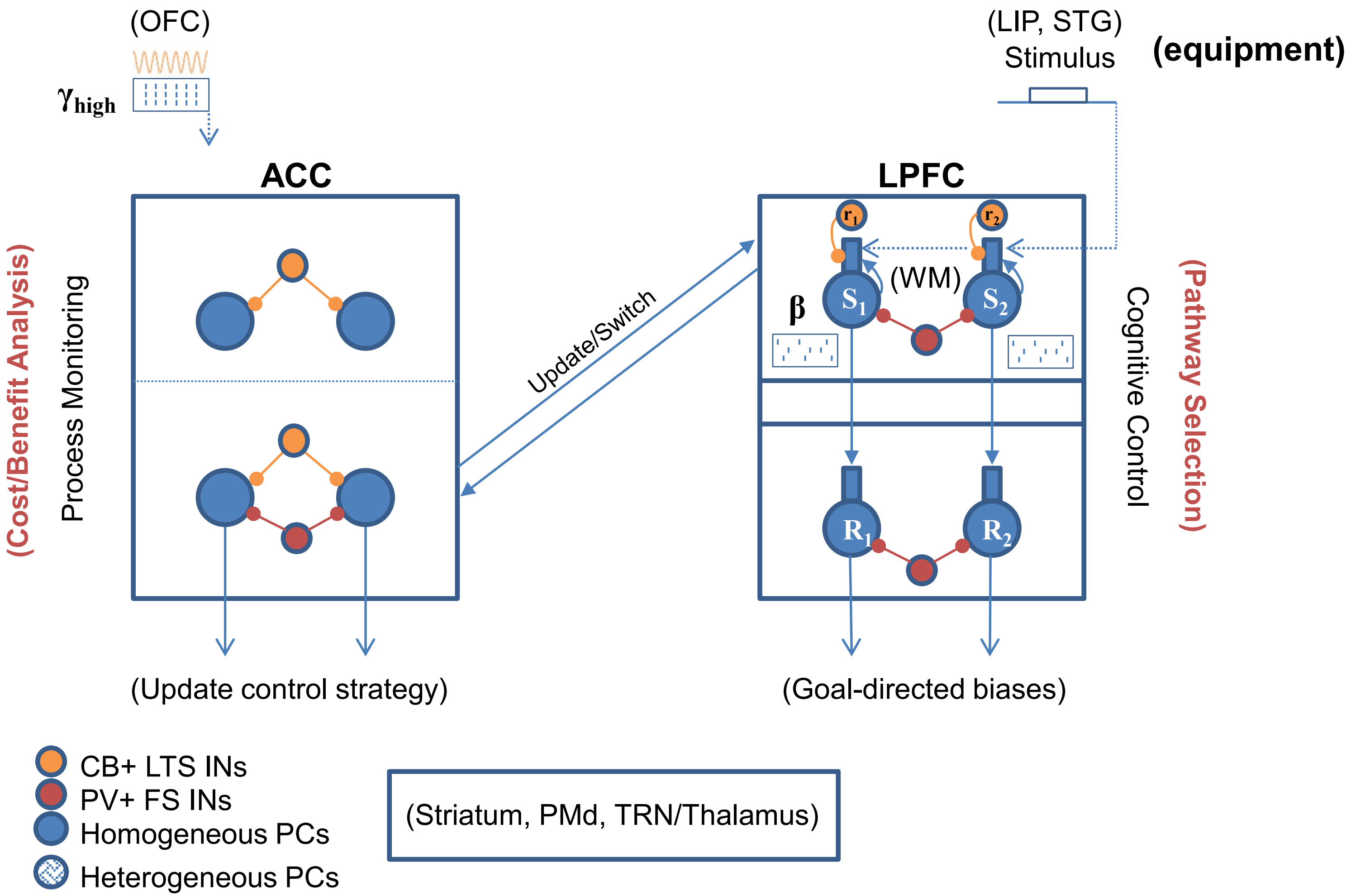
ACC/LPFC Cognitive Rhythms

Example situation: choosing between lifting weights and biking at gym.

“feel like lifting weights”

OFC values

(Weights) > (Biking)



ACC/LPFC Cognitive Rhythms

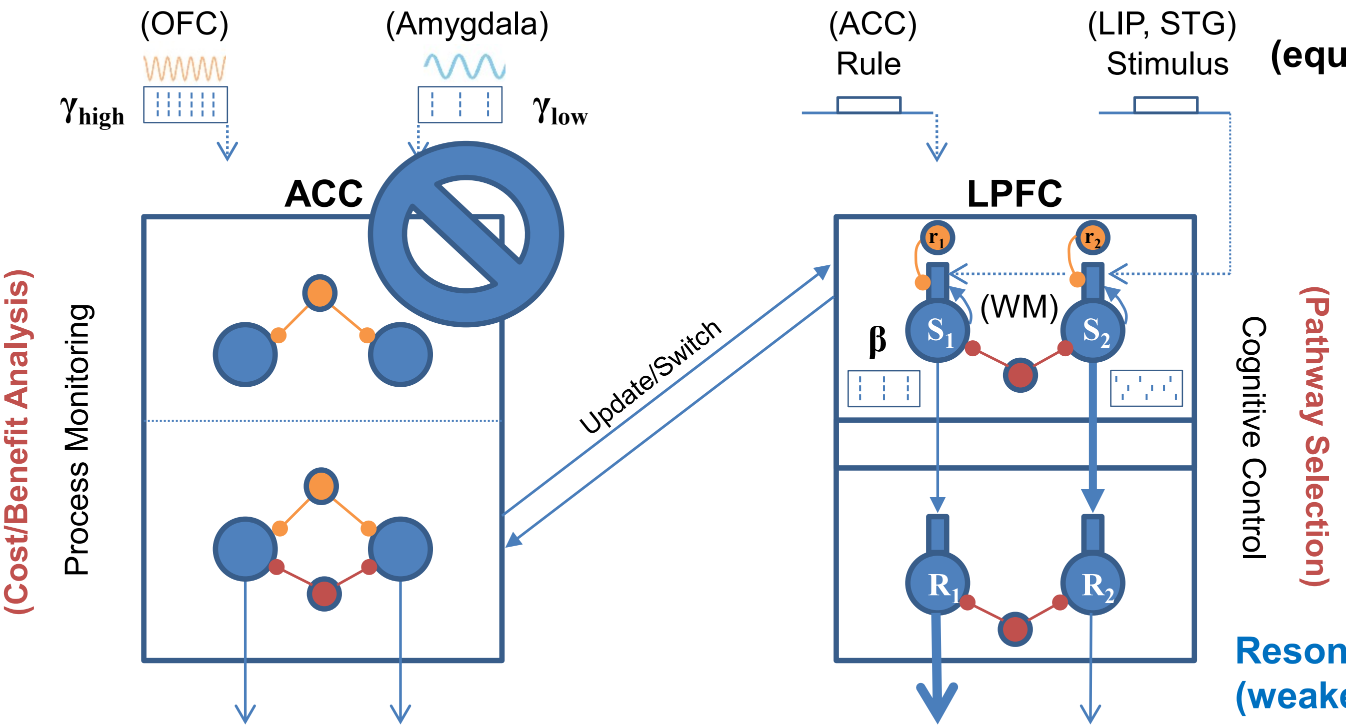
Example situation: choosing between lifting weights and biking at gym.

“feel like lifting weights”

OFC values

(Weights) > (Biking) **(Sore)** **“Weight lifting rules” (e.g., $S_1 \rightarrow R_1$)**

(equipment)



Resonance enables (weaker) mapping to produce more output

(Update control strategy)

(Goal-directed biases)

- 🟠 CB+ LTS INs
- 🔴 PV+ FS INs
- 🔵 Homogeneous PCs
- ▨ Heterogeneous PCs

(Striatum, PMd, TRN/Thalamus)

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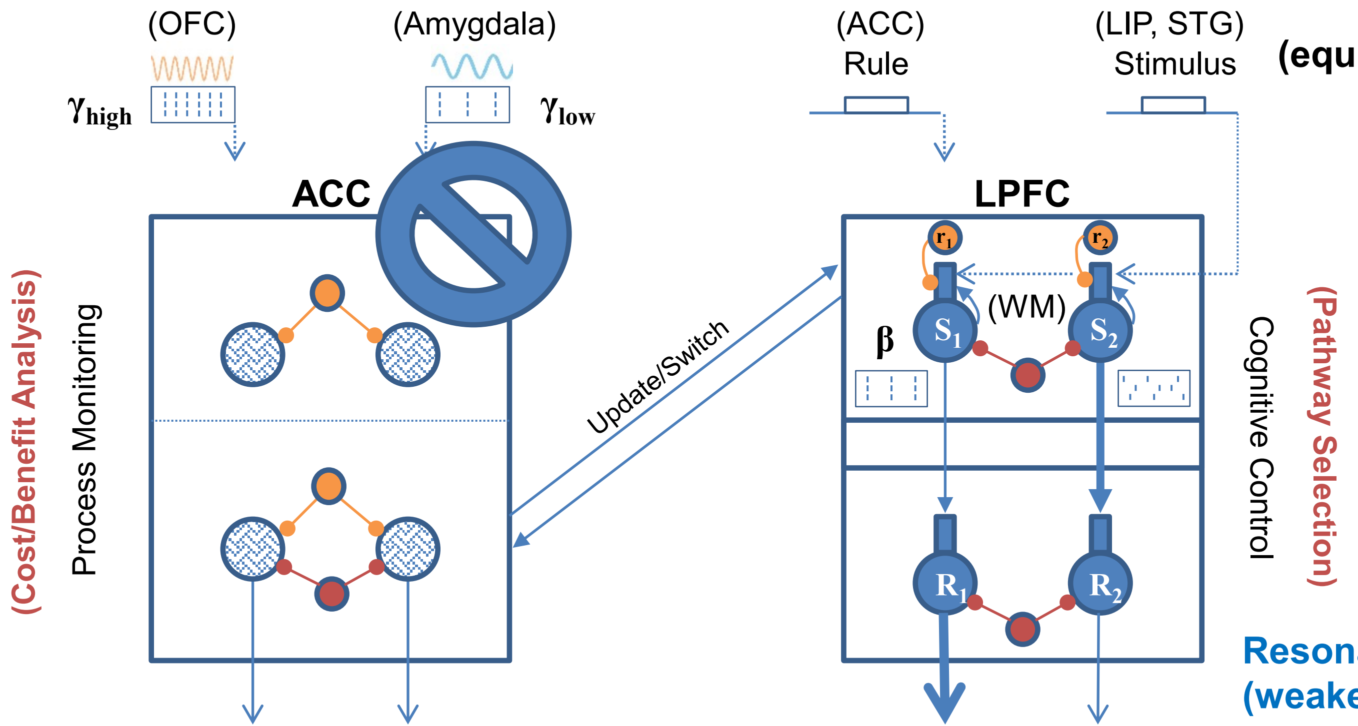

(OFC)

(Amygdala)

γ_{high}

γ_{low}

(ACC)
Rule

(LIP, STG)
Stimulus

(equipment)

ACC

LPFC

(Cost/Benefit Analysis)

Process Monitoring

Update/Switch

(WM)

β

Cognitive Control

(Pathway Selection)

(Update control strategy)

(Goal-directed biases)

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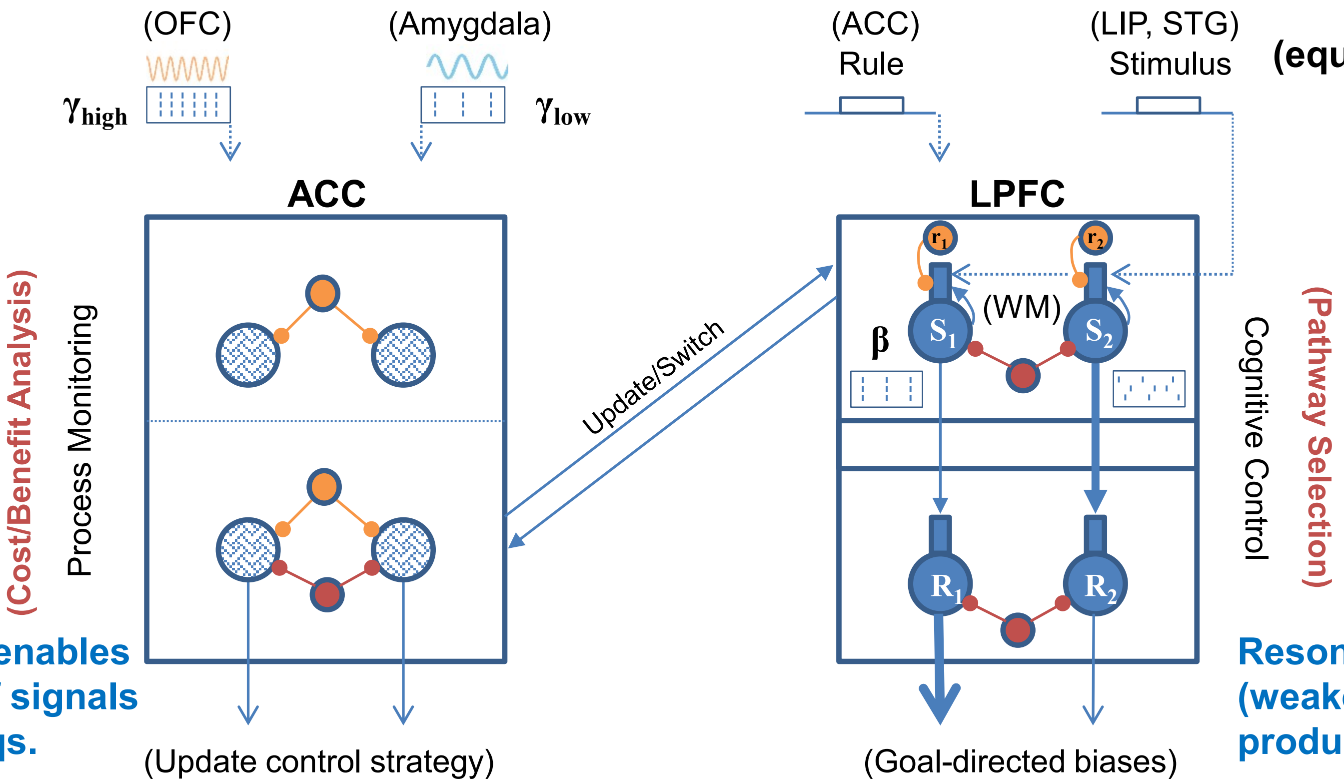

Heterogeneity enables combination of signals at different freqs.

Resonance enables (weaker) mapping to produce more output

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- ● PV+ FS INs
- ● Homogeneous PCs
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(Striatum, PMd, TRN/Thalamus)

ACC/LPFC Cognitive Rhythms

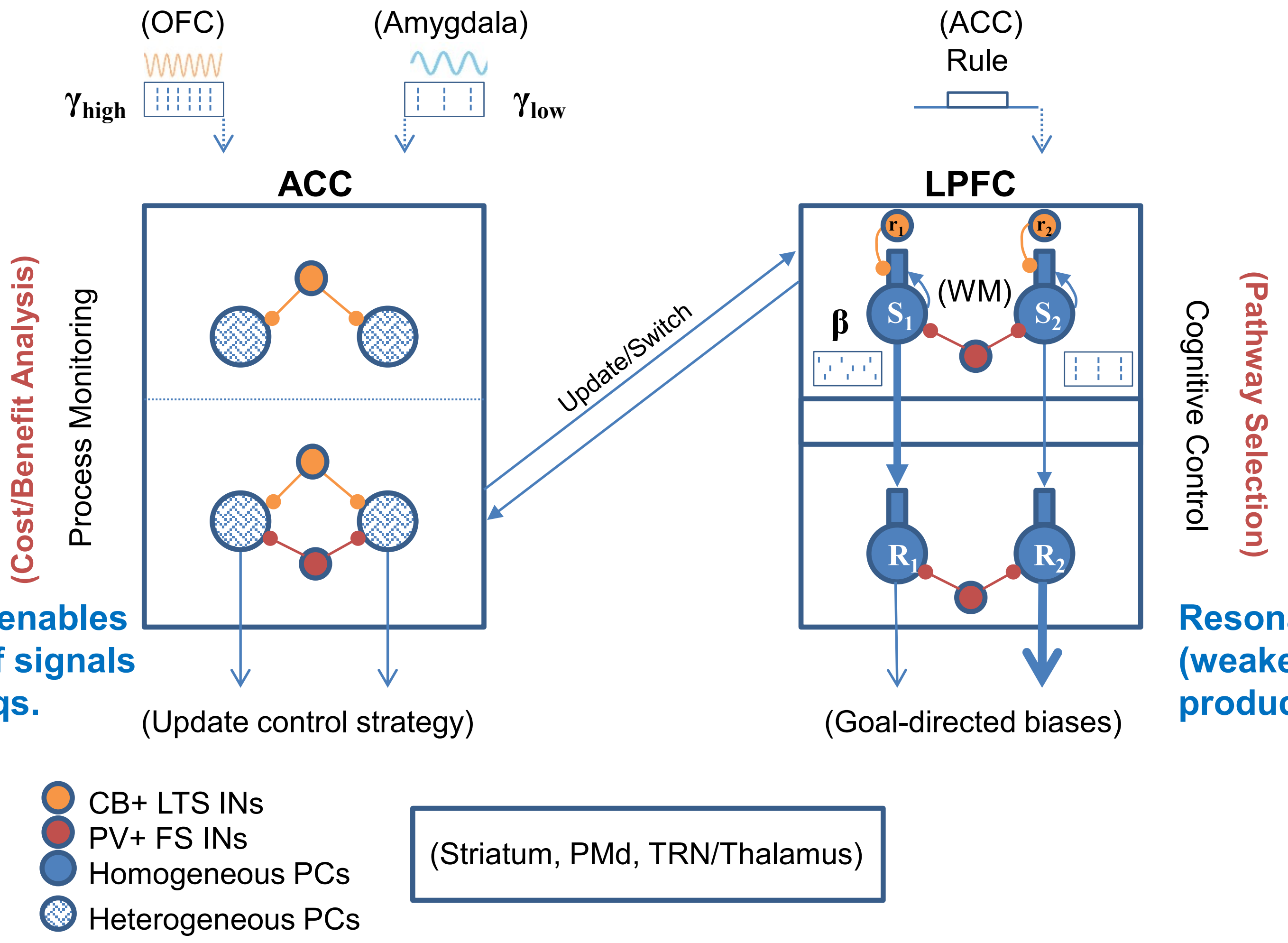
Example situation: choosing between lifting weights and biking at gym.

"feel like lifting weights"

OFC values

(Weights) > (Biking) **(Sore)**

"Biking rules" (e.g., $S_2 \rightarrow R_2$)



Heterogeneity enables combination of signals at different freqs.

Resonance enables (weaker) mapping to produce more output

** Big Picture **

- Rhythms are important in coordination (e.g., establishing functional connectivity)
- Coordination is important in cognitive control
  - LPFC: gating and routing according to rule (choice of resonant pathway)
- Cell heterogeneity decreases selectivity
  - ACC: integration of signals, updating the active rule
- Tuning heterogeneity can switch a network between selective and combinatorial processing modes

Acknowledgements

- **Nancy Kopell**

- **Fiona LeBeau**
- **Tallie Adams**
- **Miles Whittington**

- **Helen Barbas**
- **Dan Bullock**
- **Mike Hasselmo**
- **Eric Halgren**

- **Shelley Russek**
- **Sandi Grasso**

- **Salva Ardid**
- **Michelle Mccarthy**
- **Joachim Hass**

- **GPN**
- **CRC**
- **NaK**