MASTERCLASS: CNS quantitative systems biology in the research of new drugs

Presenters:
Robert Carr, In Silico Biosciences, Inc.
Athan Spiros, In Silico Biosciences, Inc.

3rd General Assembly, via ZOOM, 13th – 15th December 2021

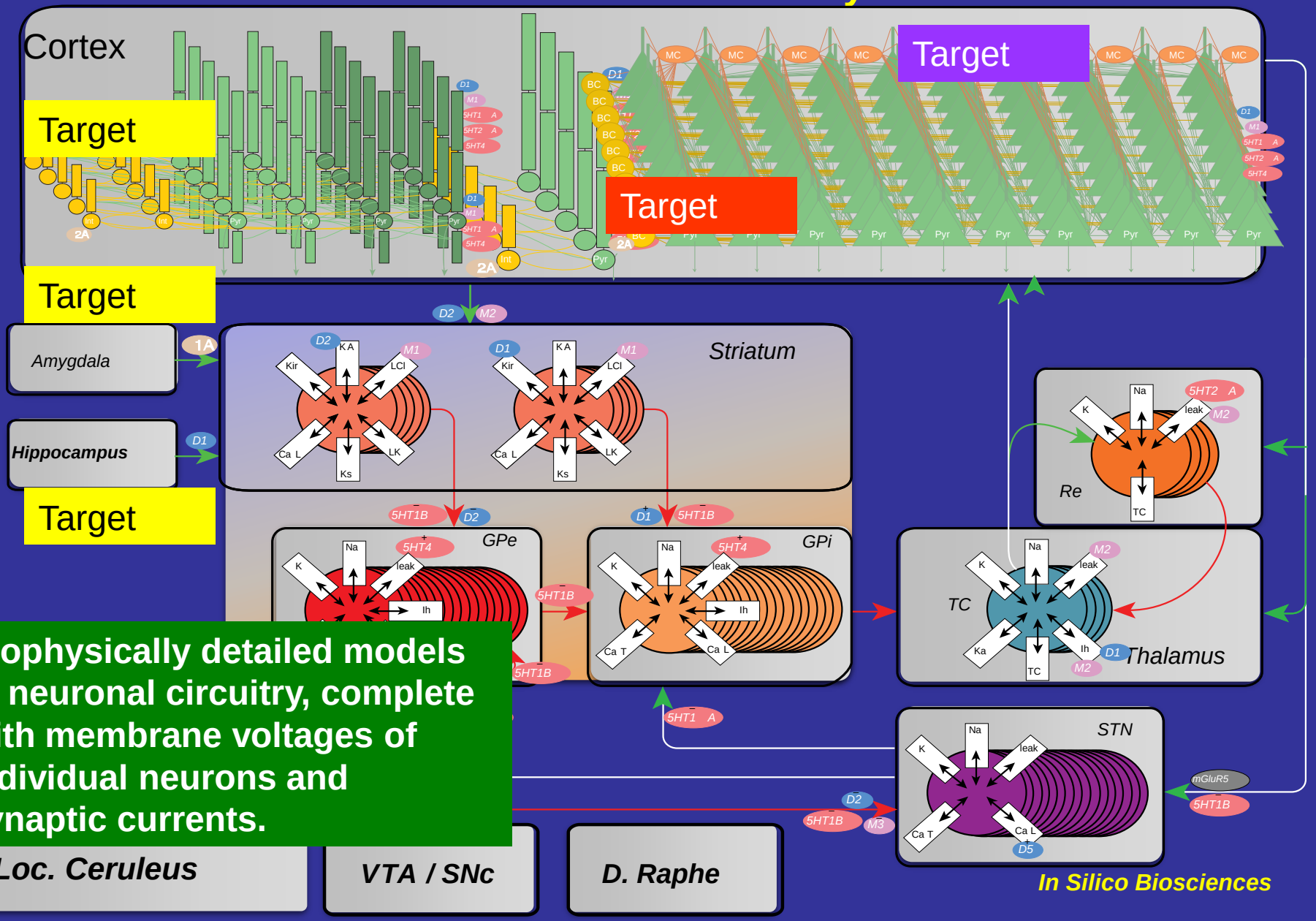
This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 848068.

CNS quantitative systems biology in the research of new drugs

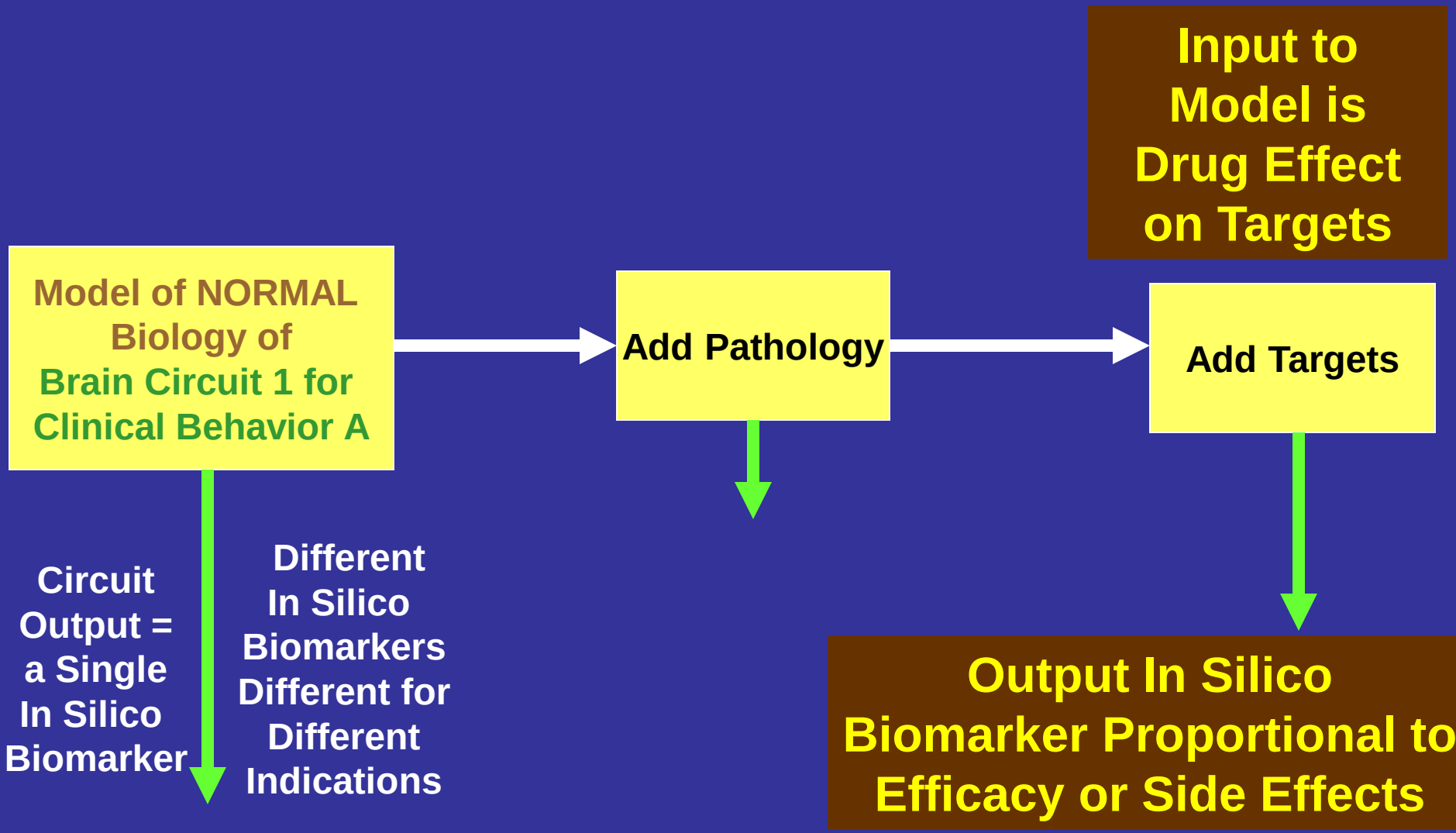
- Platform Architecture - Robert
- Reaction of Pharma towards QSP and Opportunities - Robert
- Case Study to Elaborate Technology - Athan

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 848068.

In Silico Biosciences –
Modeling Emergent Dynamics of CNS Disease Circuitry



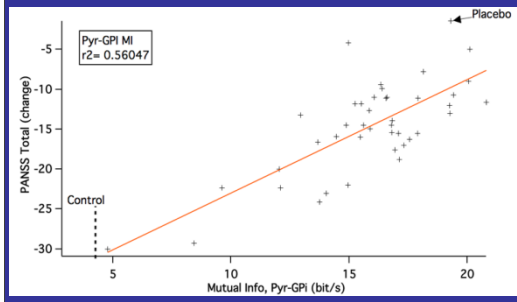
Modeling Sequence = Normal > Pathological > Drug Pharmacology (Targets)



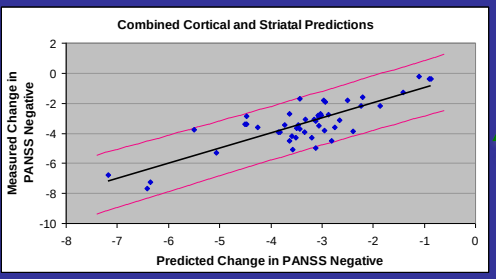
In Silico Biosciences

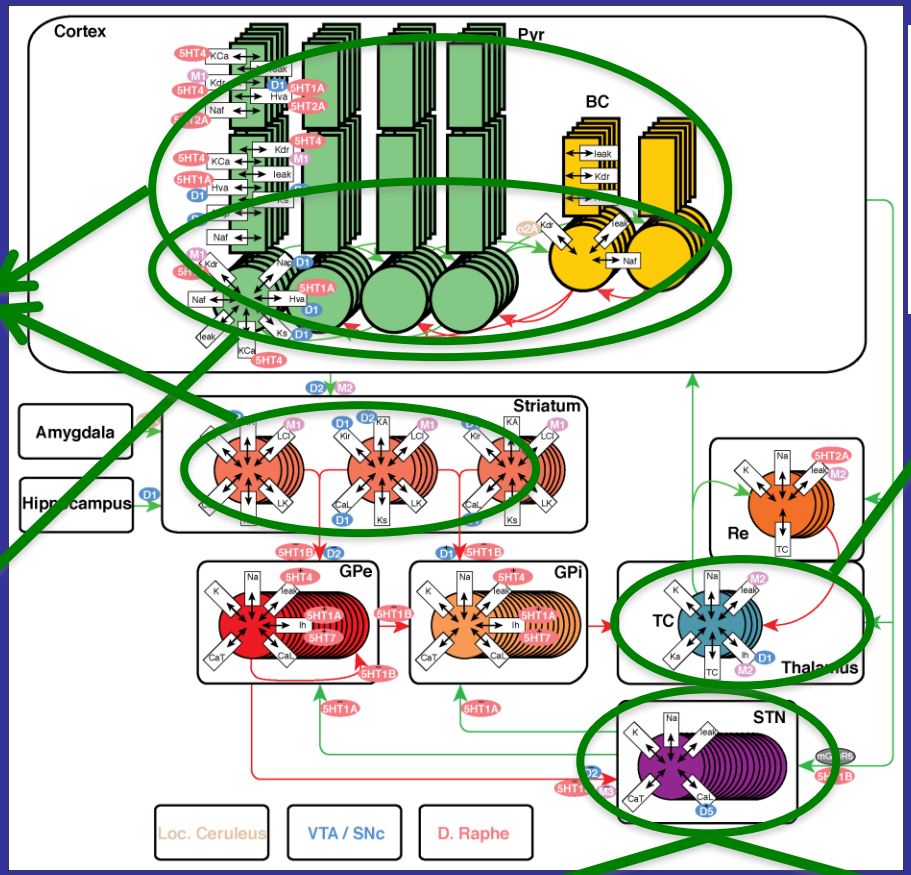
Different In Silico Biomarkers for Different Indications and Clinical Scales

PANSS Total as mutual information transfer cortex-GPI

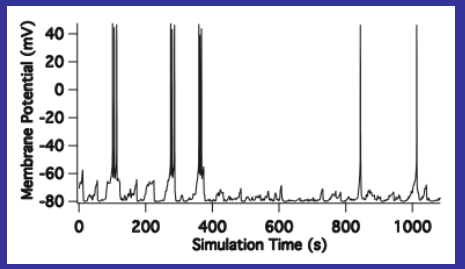


Negative PANSS are correlated with striatum and cortical excitability.

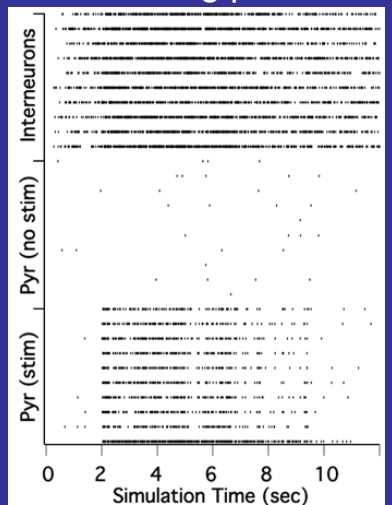




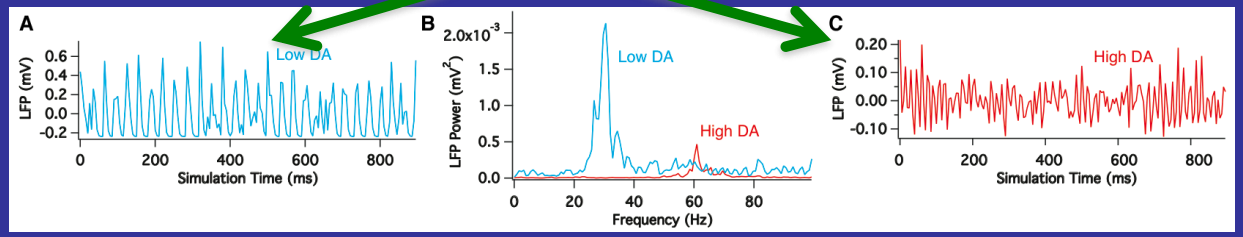
Huntington's disease symptoms are correlated with TC excitability.



Cognitive symptoms of schizophrenia are correlated dynamics of cortical firing patterns.

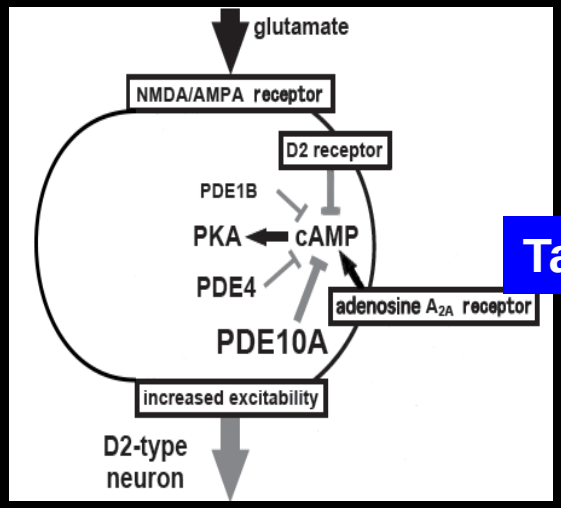


Parkinson's disease symptoms are correlated with STN rhythms.



Target; to Circuit; to Clinical Estimate

The ISB Patented Platform Architecture

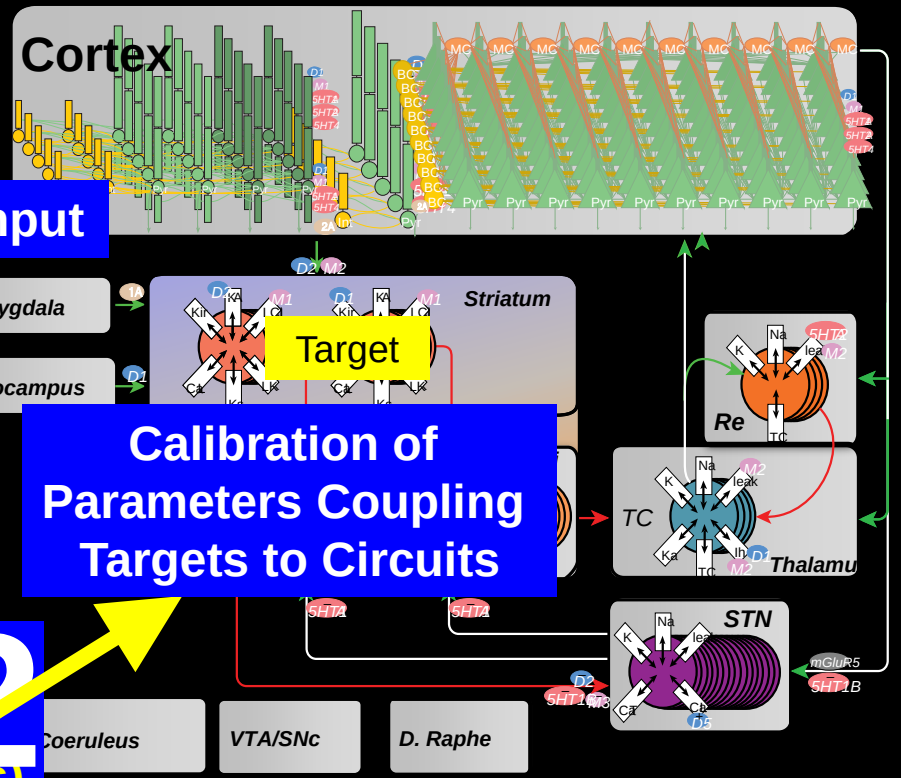


Target Activation Input

3

1

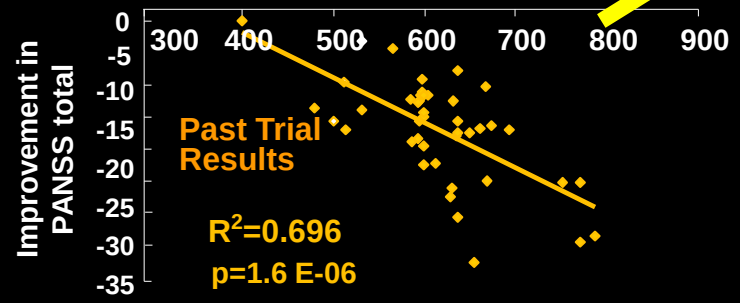
Calibration of Parameters Coupling Targets to Circuits



Neuronal Circuit Output
In Silico Biomarker
(Different for Different Indications)

2

CIRCUIT MODEL OUTPUT



Systemic model explains more of variance

- **Helps Develop Internally Consistent Systemic Physiological Hypotheses**
- **Regression Equation Enables Low Res Estimate of Clinical Effects**
- **Clinical Correlation Is a Competitive Validation Relative to Comparator**

CNS quantitative systems biology in the research of new drugs

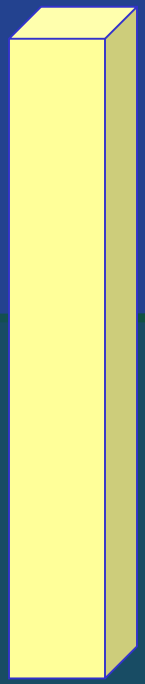
- Platform Architecture - Robert
- Reaction of Pharma to QSP and Opportunities - Robert

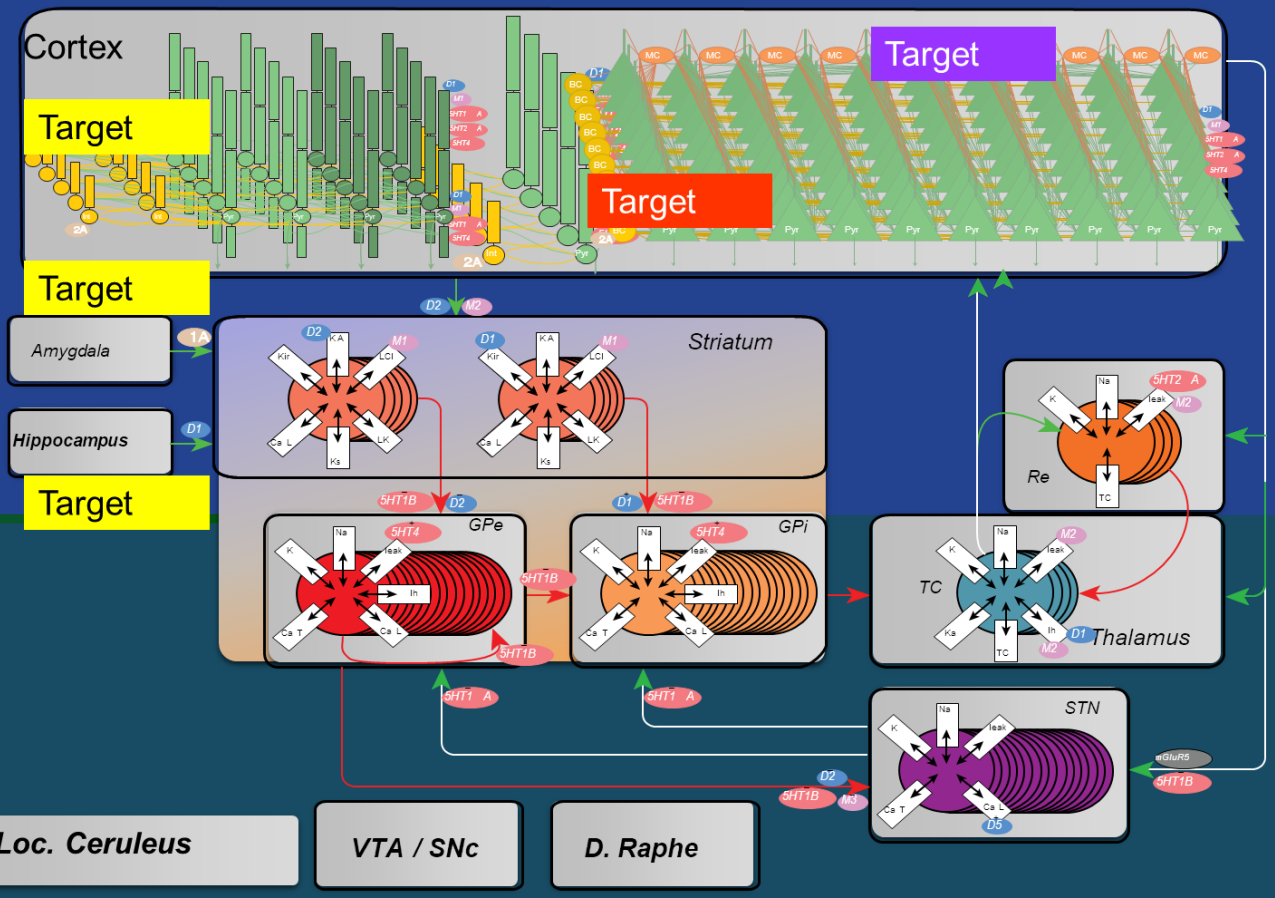
This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 848068.

Pharma Reactions to QSP

Will a Blind Man Take One Eye or Hold Out for Two?

Status Quo Systemic Predictions = Almost Blind

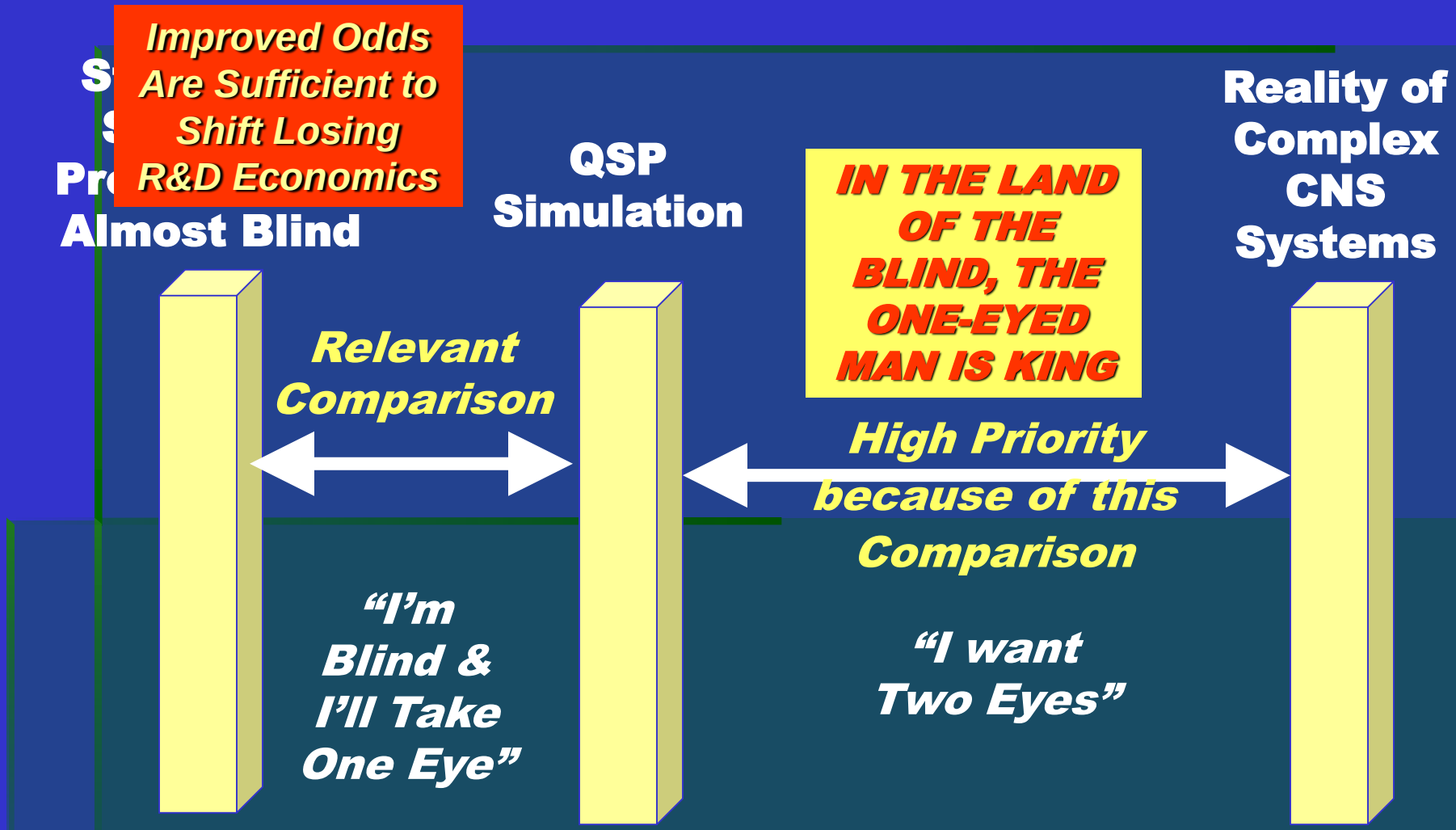




In Silico Biosciences, Inc.

Pharma Reactions to QSP

Will a Blind Man Take One Eye or Hold Out for Two?



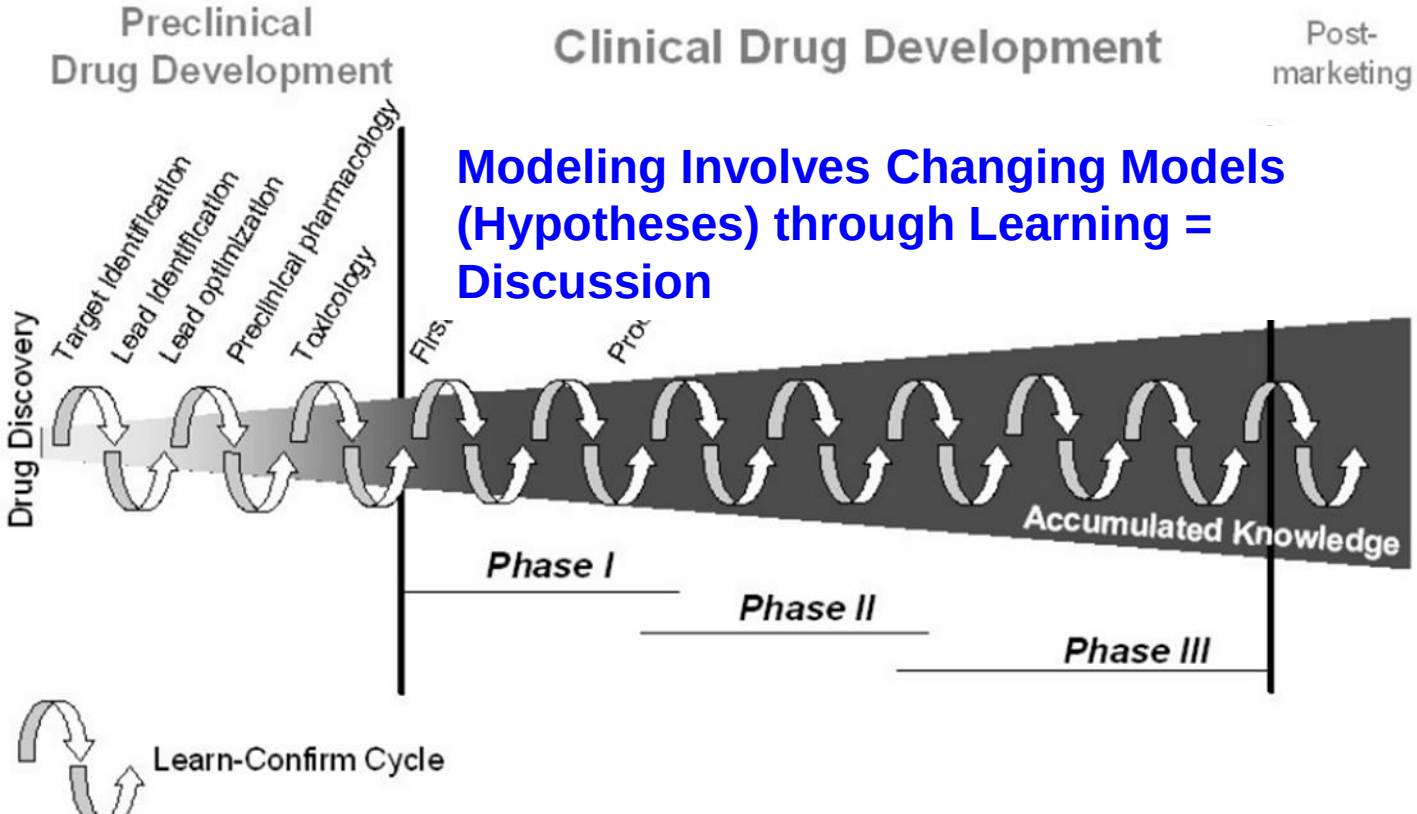
The Opportunity

Improved Odds Are Sufficient to Shift Losing R&D Economics

Game Changer

Model-Based Drug Development:

Apply Learn-Confirm Data Integration to Knowledge Paradigm Throughout R&D



Modeling Involves Changing Models (Hypotheses) through Learning = Discussion

Computational Systems Modeling (QSP) Facilitates Hypothesis Development and Refinement

"Science is built up of facts, as a house is built of stones;

but an accumulation of facts is no more a science than a heap of stones is a house."

— Henri Poincare (Science and Hypothesis)

Simulate Your Predictive Systemic Hypotheses (Model Based Drug Development) and Get One Eye in the Land of the Blind

IN THE LAND OF THE BLIND, THE ONE-EYED MAN IS KING

QSPainRelief

CNS quantitative systems biology in the research of new drugs

- ❑ Platform Architecture
- ❑ View of Pharma towards QSP and Opportunities
- ❑ Case Study to Elaborate Technology

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 848068.

Quantitative systems biology in the research of new drugs in CNS

1. Example: Cortical Model of Working Memory
2. Example: Addition of New Receptor
3. New Drug Development

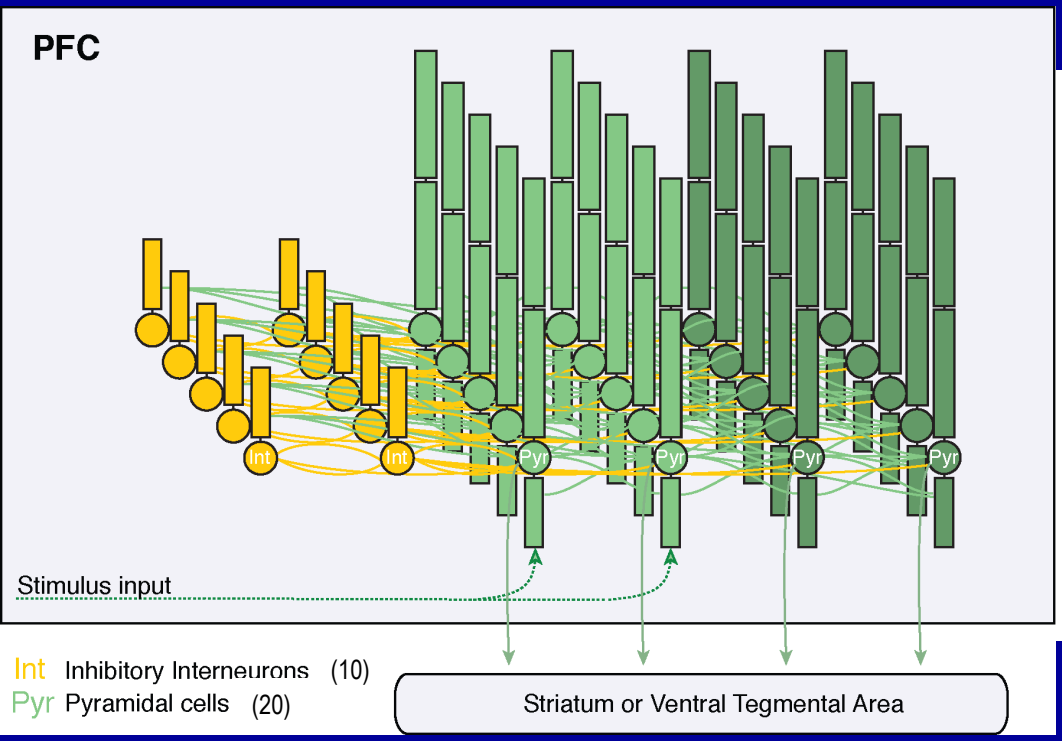
(1a) Determine The Problem

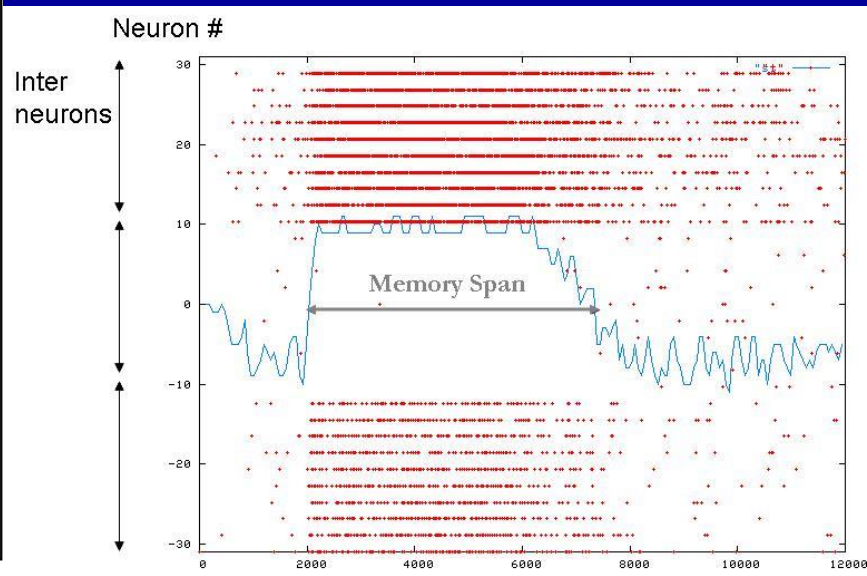
- What is the problem?
  - For what indication?
    - Working memory
  - For what kind of targets/drugs?
    - Dopamine and serotonin receptors
- What data is available?
  - % Correct in 2-back WM test
  - For COMT genotype (affects dopamine)
  - For antipsychotics in patients with schizophrenia

Geerts et al. Nature CPT: Pharmacometrics and Systems Pharmacology (2013), 2; e36.

(1b) Determine an Appropriate Neuronal Model

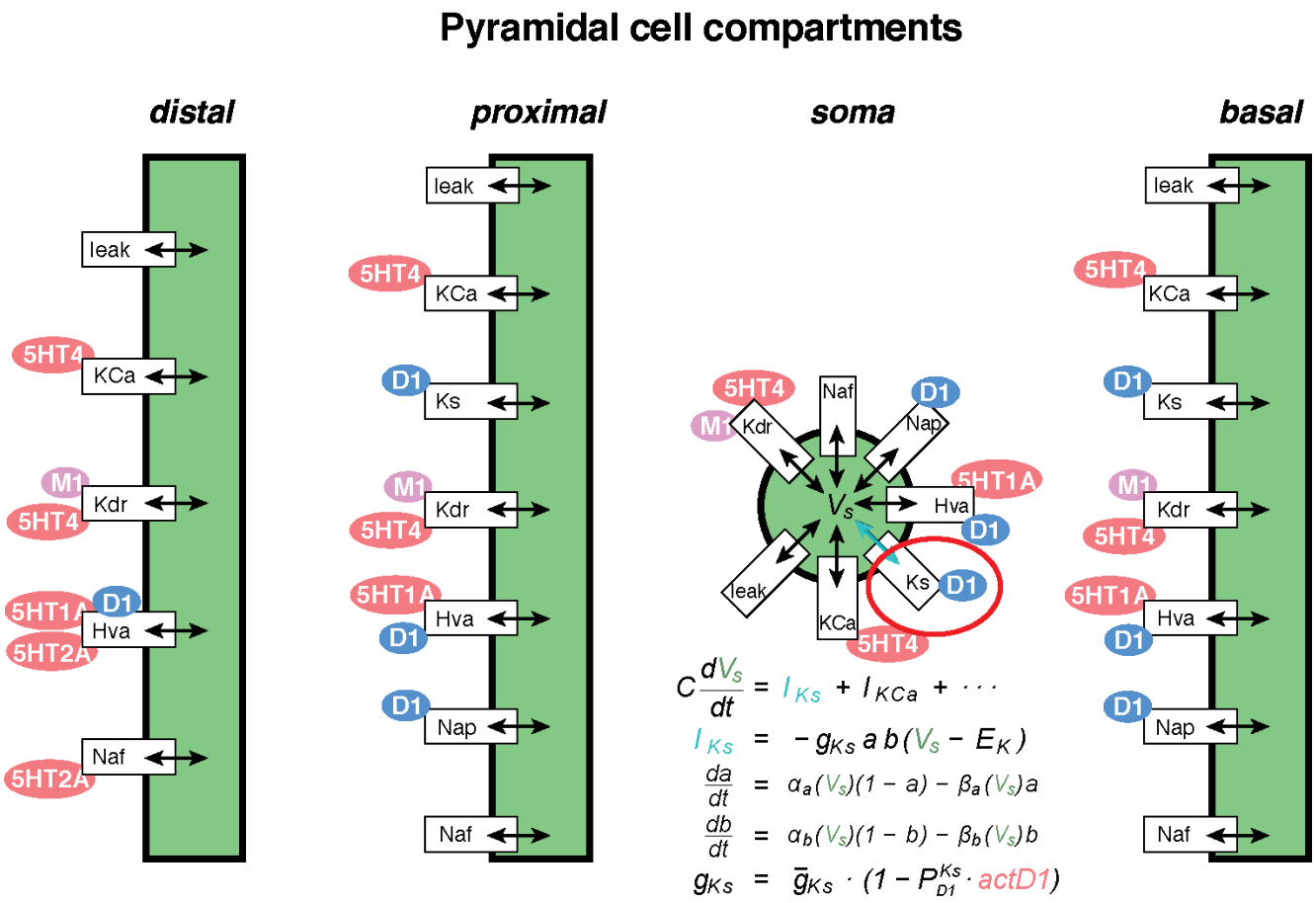
- A model may already exist

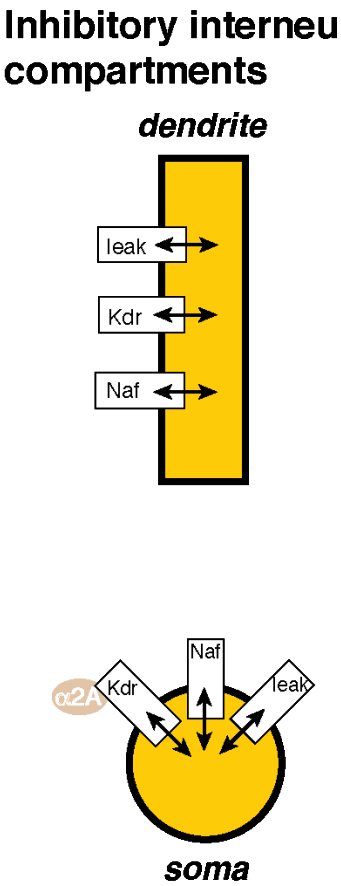




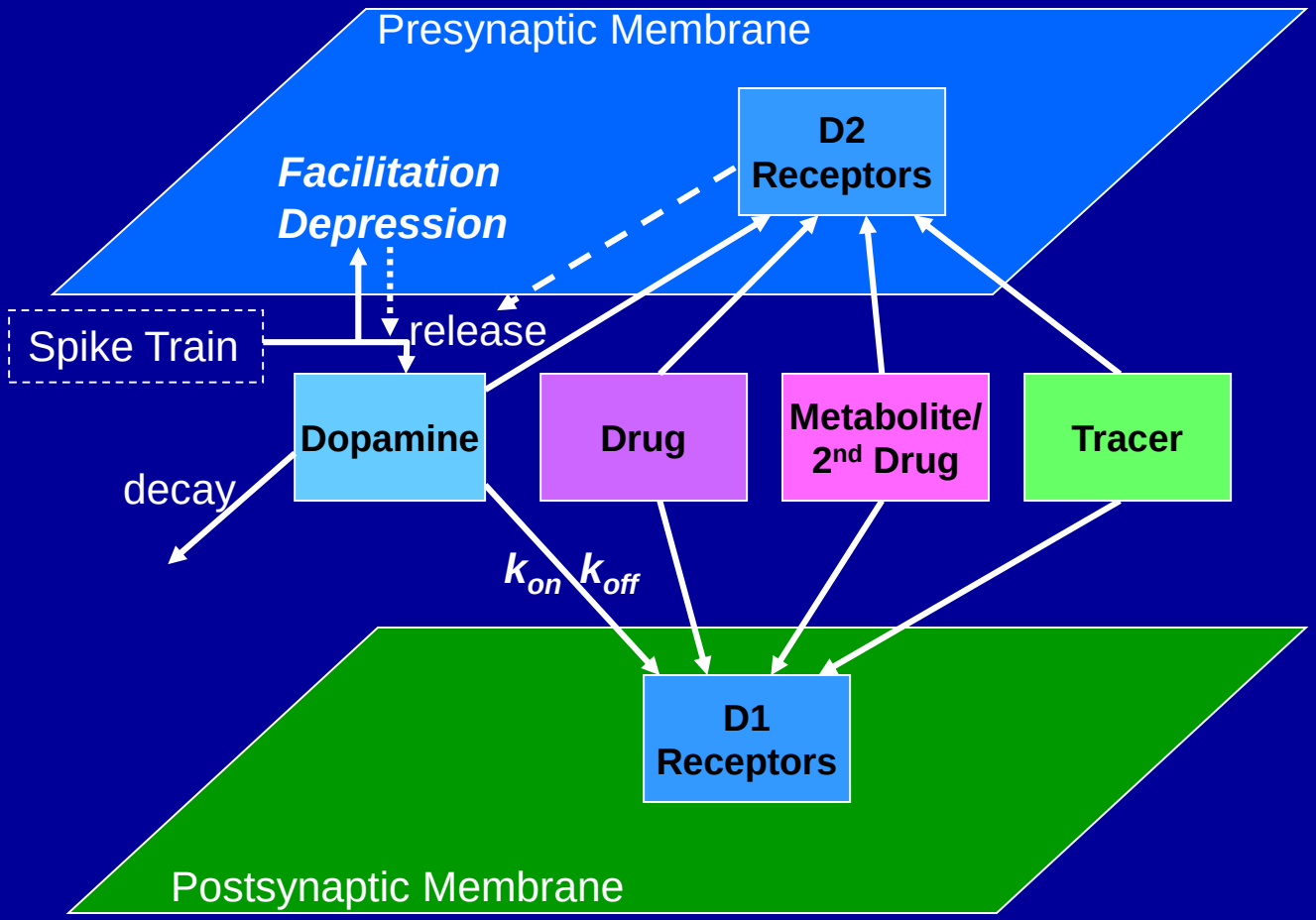
Durstewitz et al. Journal of Neurophysiology (2000) 83(3):1733-50.

(1c) Determine the Target Effects on Neurons





(1d) Determine Drug Effects (Synaptic Cleft Simulation)



Primary Inputs
- Dopamine firing
- Dopamine half-life
- Drug: Amount, Affinity, Partial Agonism
- Metabolite: Amount, Affinity, Partial Agonism
- Tracer: Amount, Affinity

Primary Readouts
- D1: Binding by dopamine, drug and tracer
- D1: "Activation"

Spiros et al, Neuropsychiatric Disease & Treatment (2010) 6: 1-15.

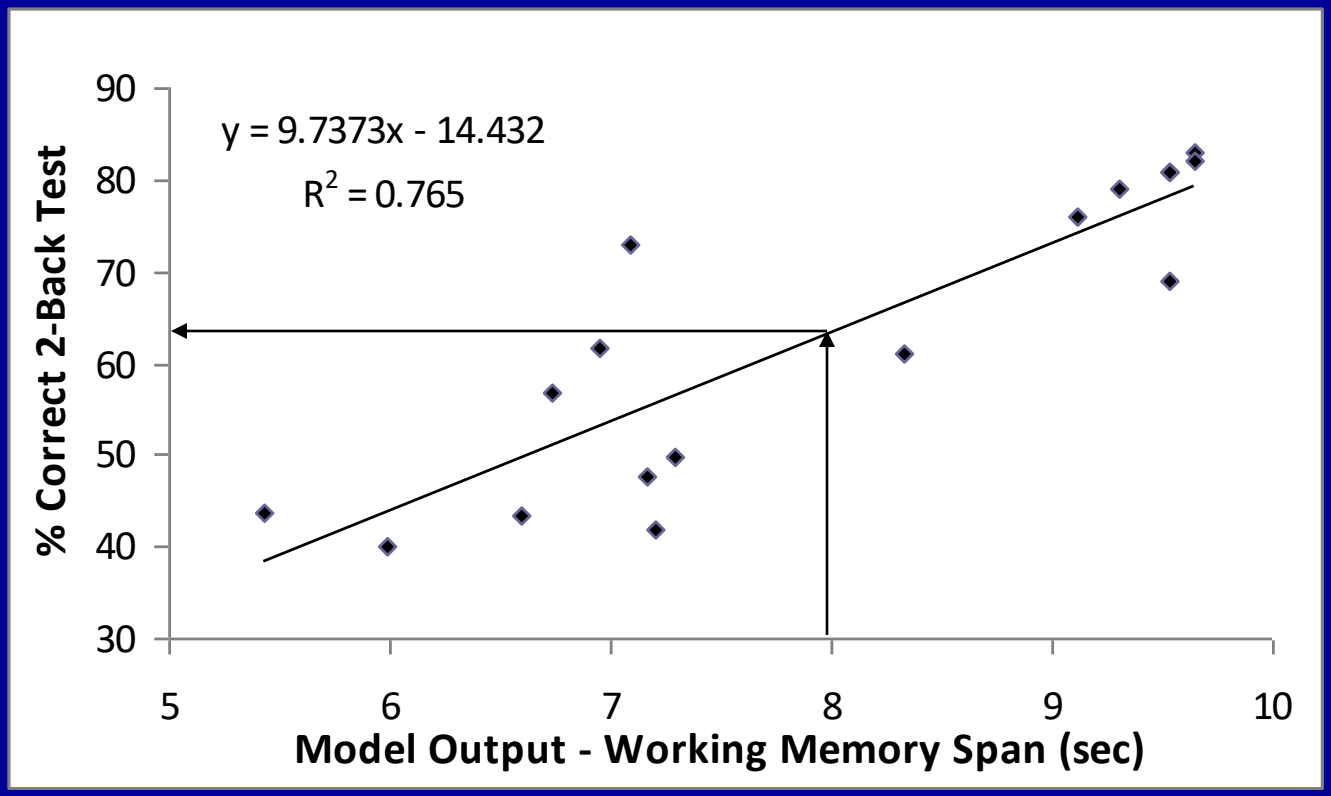
(2a) Example of Calibrating D1 Receptor Effect on Ks

$$g_{Ks} = \bar{g}_{Ks} \cdot \left(1 - P_{D1}^{Ks} \cdot actD1\right)$$

Coupling Parameter Receptor Activation

- *actD1 is the D1 activation relative to control*
  - Allows one to attain different values for all drug-doses
- Coupling parameter, *P*, is altered to get best fit
  - The parameter is initialized to the pre-clinical value: 0.3 (Dong & White, 2003)
  - The calibrated value is 0.367

(2b) Calibrate the Model



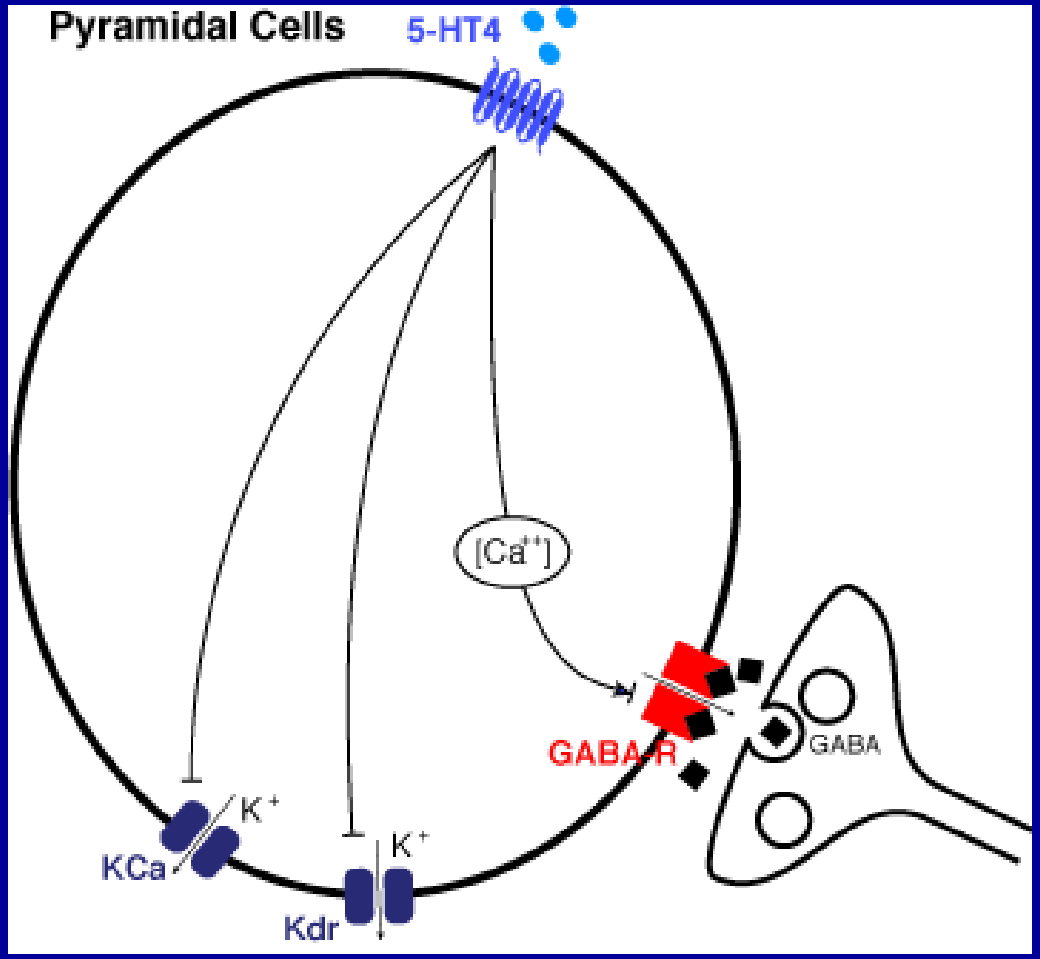
- Each point represents a drug/dose model output (x) and clinical outcome (y).
- Different sets of coupling parameters will shift points left or right (and need to be biologically constrained).
- The relationship established determines the clinical prediction of model outcomes.

(2c) Get Confidence with the Model

- Can it be validated?
  - New results might have become available.
  - Maybe some results were held back from the calibration process.
- Do model predictions make sense?
  - E.g. Is the dose reponse curve for a drug qualitatively correct?

(3) Introduce New Receptor Effect(s)

(3a) Research New Receptor Effects



Example: 5-HT4 Receptor

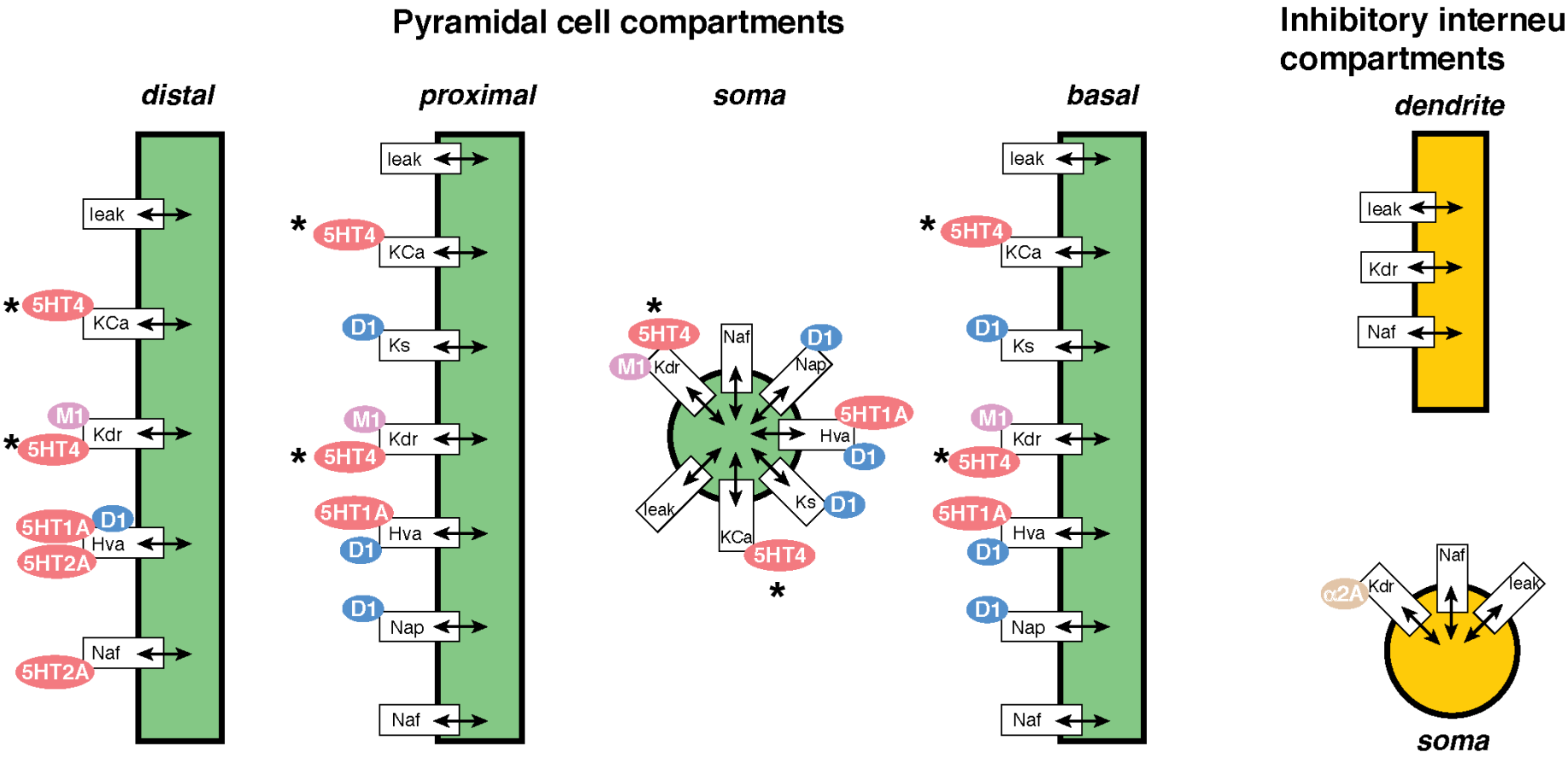
Has an effect on

- Kdr channel – max 5-HT4 activation reduces gKdr by 50%.
- KCa channel – this 5-HT4 effect is half as strong as Kdr.
- GABA-R conductance affected with a range of ±20%.

Nicholas et al. Advances in Alzheimer's Disease (2013) 2(3): 83-98.

(3b) Incorporate New Effects in the Model

5-HT4 receptors are co-localized with 5-HT1A receptors



(3c) Result of New Receptor Incorporation

- When effects were incorporated, the model showed as 5-HT4 activation increased cognition improved.
- Unfortunately for the project that we were involved with, they had created a compound that was a functional antagonist.
  - As shown in the synaptic cleft simulation.
- When the compound was tested in healthy volunteers at a cognitive deficit due to scopolamine, the compound worsened the working memory outcome at a low dose.

(4a) New Drugs: What Insights are Gained with the Modelling?

- A sensitivity analysis is very useful
- Determines
  - most important modes of action (MoA)
  - areas in need of further model refinement
  - possible leads for drug development

(4b) What Does the Model Predict for Existing Drugs?

- Use the model to **predict outcomes** of a battery of known drugs
  - Ex1: If a pharmaceutical company has a library of compounds, the ones that are applicable to the model can be simulated
  - Ex2: Can look at publicly available data for compounds that affect Receptors X, Y and Z and determine their predicted outcomes
- One can explore combination of treatments, a more straight-forward process in silico

Conclusions

- A good model is **reusable** and **refinable**
- By modelling **biological processes**, one can explore more interventions than originally imagined
  - This goes beyond “black box” calculations and relational associations
  - New modes of action can be considered at different levels of the model
    - Effects at synapses such as receptors and transporters
    - Effects at channels such as channel blockers
    - Effects at neurons such as deep brain stimulation
- All of these considerations allow one to explore new drug development and make predictions to be tested further