Deep hybrid modeling of a HEK293 process: combining Long Short-Term Memory (LSTM) networks with first principles equations

Rui Oliveira[1], João R. C. Ramos[1], José Pinto[1], Gil Poiares-Oliveira[1], Ludovic Peeters[2], and Patrick Dumas[2]

[1]Universidade NOVA de Lisboa Faculdade de Ciencias e Tecnologia
[2]GlaxoSmithKline Biologicals SA Rixensart

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Abstract

In this paper, Long Short-Term Memory (LSTM) networks and multilayered feedforward neural networks (FFNNs) were combined with first principles equations in a hybrid workflow to describe human embryonic kidney 293 (HEK293) culture dynamics. Experimental data of 27 extracellular state variables in 20 fed-batch HEK293 cultures were collected in a parallel high throughput 250 mL cultivation system. The adaptive moment estimation method (ADAM) with stochastic regularization and cross-validation were employed for deep learning. A total of 784 hybrid models with varying deep neural network (DNN) architectures, depths, layers sizes and node activation functions were compared. In most scenarios, hybrid LSTM models outperformed hybrid FFNN models in terms of training and testing error. Hybrid LSTM models revealed to be less sensitive to data resampling than FFNN hybrid models. As disadvantages, Hybrid LSTM models are in general more complex (higher number of parameters) and have a higher computation cost than FFNN hybrid models. The hybrid model with the highest prediction accuracy consisted in a LSTM network with 7 internal states connected in series with dynamic material balance equations. This hybrid model correctly predicted the dynamics of the 27 state variables (R^2=0.93 in the test data set), including biomass, key substrates, amino acids and metabolic by-products for around 10 cultivation days.

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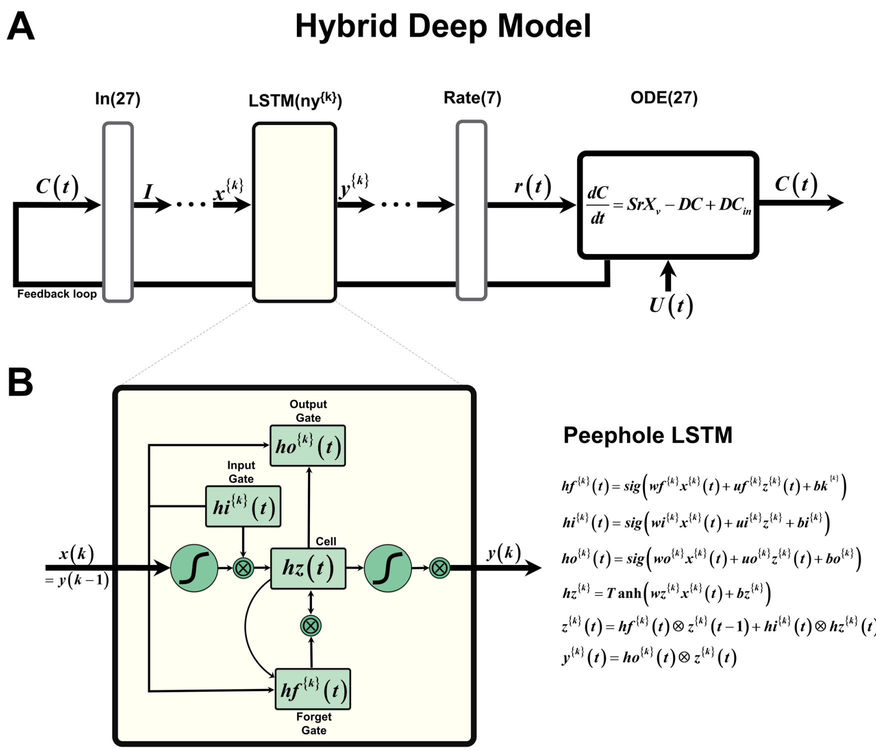
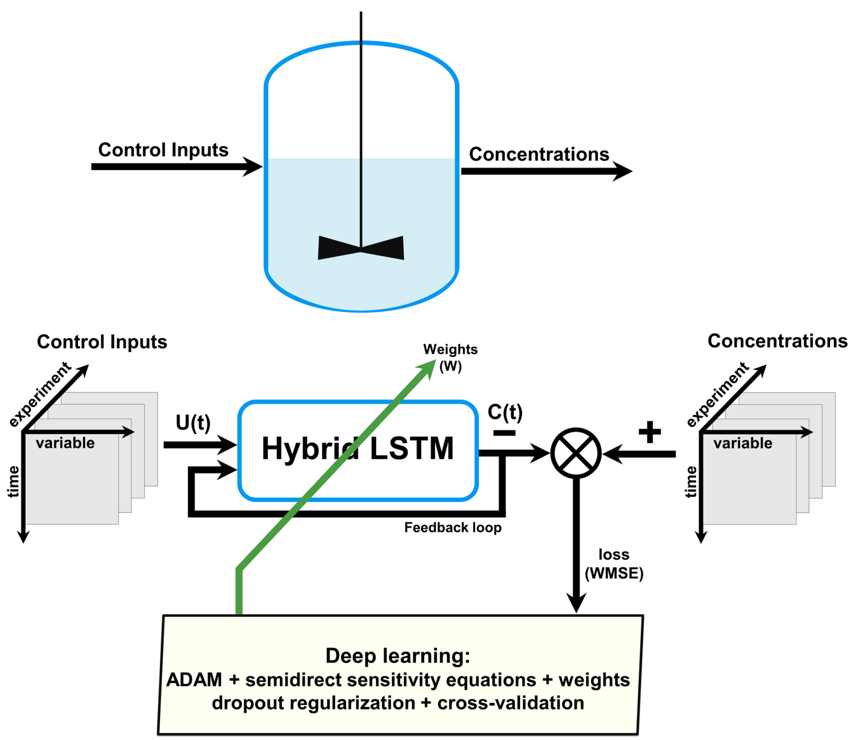
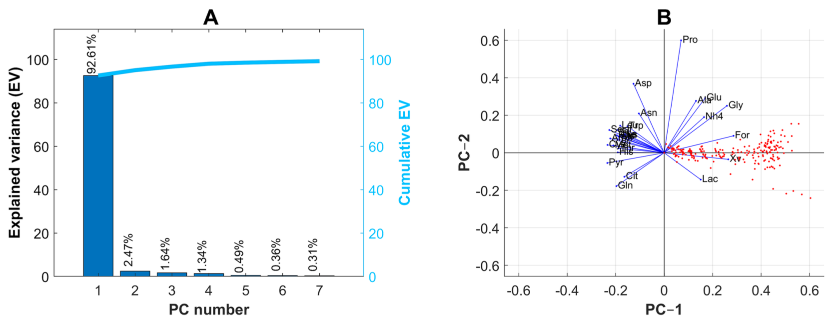
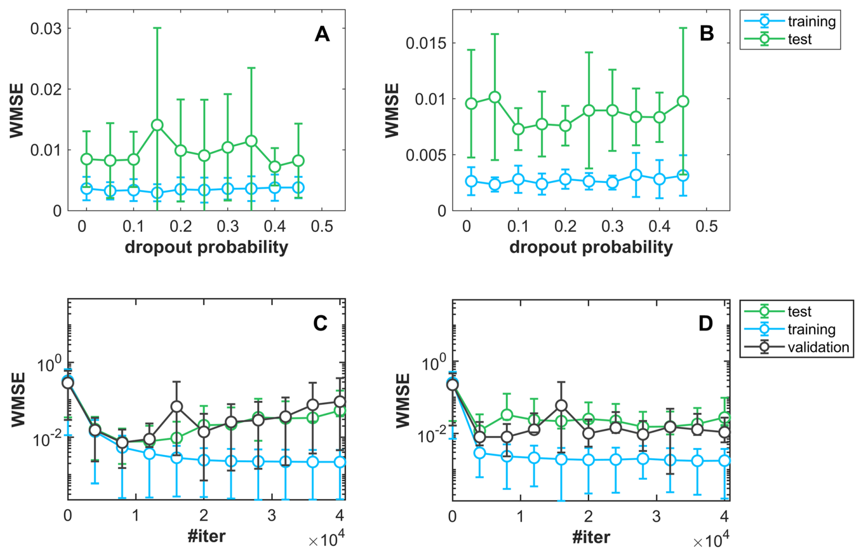
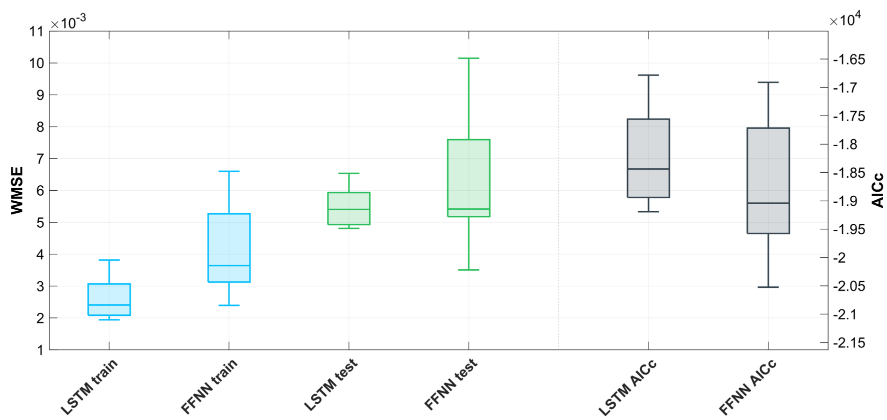

A
Hybrid Deep Model
In(27)
LSTM(ny^{k})
Rate(7)
ODE(27)
$C(t)$
I
$x^{\{k\}}$
$y^{\{k\}}$
$r(t)$
$\frac{dC}{dt} = SrX_v - DC + DC_{in}$
$C(t)$
Feedback loop
$U(t)$
B
Output Gate
$ho^{\{k\}}(t)$
Input Gate
$hi^{\{k\}}(t)$
Cell
$hz(t)$
$x(k) = y(k-1)$
$y(k)$
$hf^{\{k\}}(t)$
Forget Gate
Peephole LSTM
$hf^{\{k\}}(t) = sig\left(wf^{\{k\}}x^{\{k\}}(t) + uf^{\{k\}}z^{\{k\}}(t) + bk^{\{k\}}\right)$
$hi^{\{k\}}(t) = sig\left(wi^{\{k\}}x^{\{k\}}(t) + ui^{\{k\}}z^{\{k\}} + bi^{\{k\}}\right)$
$ho^{\{k\}}(t) = sig\left(wo^{\{k\}}x^{\{k\}}(t) + uo^{\{k\}}z^{\{k\}}(t) + bo^{\{k\}}\right)$
$hz^{\{k\}} = T\text{anh}\left(wz^{\{k\}}x^{\{k\}}(t) + bz^{\{k\}}\right)$
$z^{\{k\}}(t) = hf^{\{k\}}(t) \otimes z^{\{k\}}(t-1) + hi^{\{k\}}(t) \otimes hz^{\{k\}}(t)$
$y^{\{k\}}(t) = ho^{\{k\}}(t) \otimes z^{\{k\}}(t)$


Control Inputs
Concentrations
Control Inputs
experiment
variable
time
U(t)
Hybrid LSTM
Weights (W)
C(t)
−
+
Feedback loop
loss (WMSE)
Concentrations
experiment
variable
time
Deep learning:
ADAM + semidirect sensitivity equations + weights
dropout regularization + cross-validation


A
B
Explained variance (EV)
Cumulative EV
PC number
92.61%
2.47%
1.64%
1.34%
0.49%
0.36%
0.31%
PC−1
PC−2
Pro
Asp
Glu
Ala
Gly
Nh4
Asn
For
Pyr
Cit
Gln
Lac
Xv

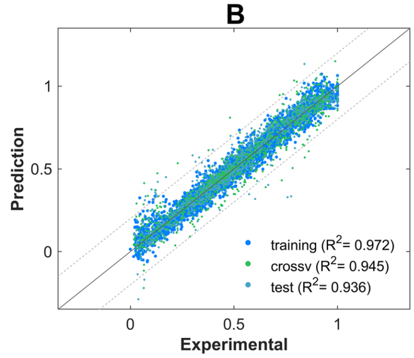

A
B
C
D
WMSE
dropout probability
#iter
training
test
validation


WMSE
AICc
LSTM train
FFNN train
LSTM test
FFNN test
LSTM AICc
FFNN AICc

A

Partition	WMSE train	WMSE test	R^2 train	R^2 test
1	3.07E-03	4.81E-03	0.96	0.94
2	2.59E-03	4.87E-03	0.97	0.94
3	2.05E-03	4.97E-03	0.97	0.94
4	3.82E-03	4.93E-03	0.95	0.94
5	3.76E-03	5.25E-03	0.95	0.93
6	2.22E-03	6.37E-03	0.97	0.93
7	2.73E-03	5.56E-03	0.96	0.93
8	2.12E-03	5.93E-03	0.97	0.93
9	1.94E-03	6.54E-03	0.97	0.92
10	2.08E-03	5.87E-03	0.97	0.93
Mean	2.64E-03	5.51E-03	0.97	0.93
SD	7.01E-04	6.40E-04	0.01	0.01
CV (%)	24.02	10.51	0.82	0.57

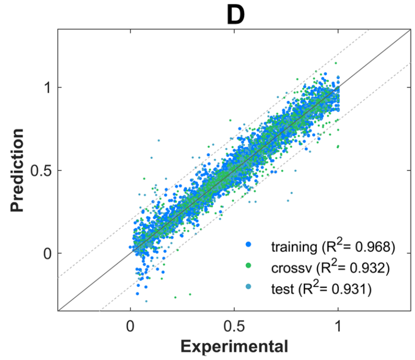
B

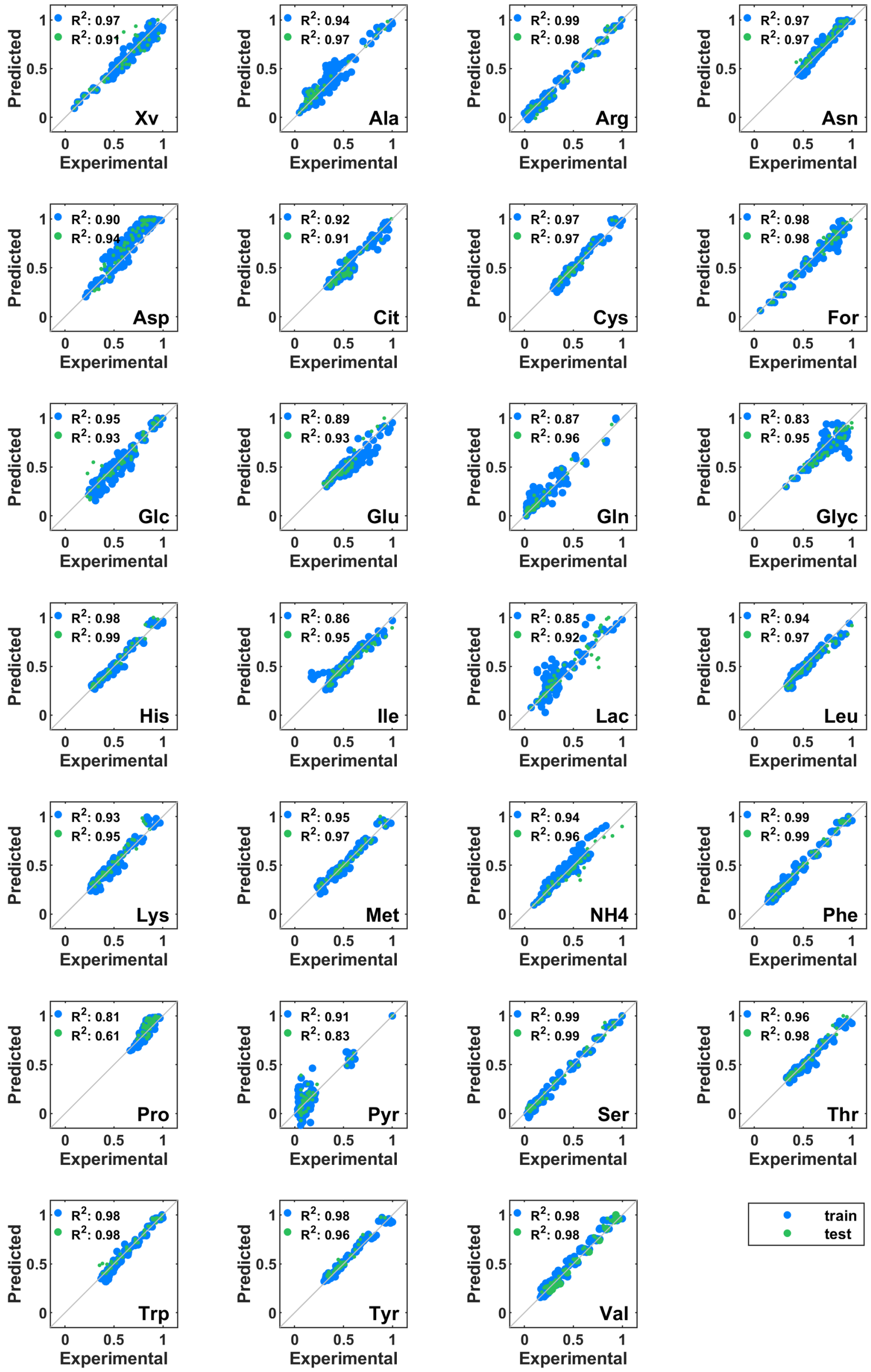


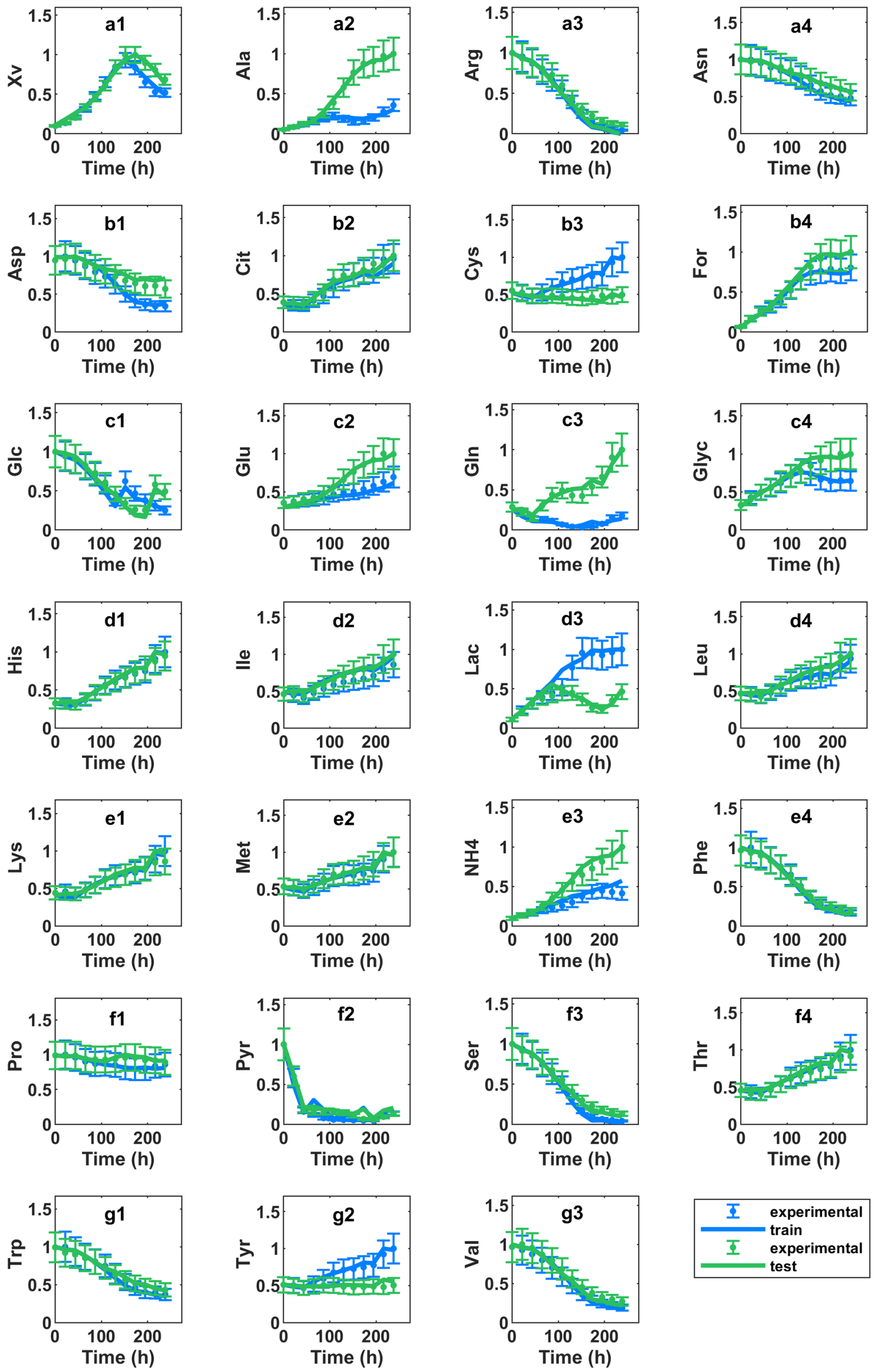
C

Partition	WMSE train	WMSE test	R^2 train	R^2 test
1	3.29E-03	7.59E-03	0.96	0.91
2	3.13E-03	5.36E-03	0.96	0.93
3	2.72E-03	1.01E-02	0.96	0.88
4	3.37E-03	5.25E-03	0.96	0.93
5	5.27E-03	3.51E-03	0.93	0.95
6	3.92E-03	4.88E-03	0.95	0.94
7	6.60E-03	9.75E-03	0.92	0.88
8	5.86E-03	6.46E-03	0.92	0.92
9	2.40E-03	5.47E-03	0.97	0.93
10	4.04E-03	5.18E-03	0.95	0.94
Mean	4.06E-03	6.36E-03	0.95	0.92
SD	1.40E-03	2.16E-03	0.02	0.02
CV (%)	31.25	30.76	1.65	2.44

D




R^2: 0.97
R^2: 0.91
Xv
R^2: 0.94
R^2: 0.97
Ala
R^2: 0.99
R^2: 0.98
Arg
R^2: 0.97
R^2: 0.97
Asn
R^2: 0.90
R^2: 0.94
Asp
R^2: 0.92
R^2: 0.91
Cit
R^2: 0.97
R^2: 0.97
Cys
R^2: 0.98
R^2: 0.98
For
R^2: 0.95
R^2: 0.93
Glc
R^2: 0.89
R^2: 0.93
Glu
R^2: 0.87
R^2: 0.96
Gln
R^2: 0.83
R^2: 0.95
Glyc
R^2: 0.98
R^2: 0.99
His
R^2: 0.86
R^2: 0.95
Ile
R^2: 0.85
R^2: 0.92
Lac
R^2: 0.94
R^2: 0.97
Leu
R^2: 0.93
R^2: 0.95
Lys
R^2: 0.95
R^2: 0.97
Met
R^2: 0.94
R^2: 0.96
NH4
R^2: 0.99
R^2: 0.99
Phe
R^2: 0.81
R^2: 0.61
Pro
R^2: 0.91
R^2: 0.83
Pyr
R^2: 0.99
R^2: 0.99
Ser
R^2: 0.96
R^2: 0.98
Thr
R^2: 0.98
R^2: 0.98
Trp
R^2: 0.98
R^2: 0.96
Tyr
R^2: 0.98
R^2: 0.98
Val
Predicted
Experimental
0
0.5
1
train
test



a1
Xv
a2
Ala
a3
Arg
a4
Asn
b1
Asp
b2
Cit
b3
Cys
b4
For
c1
Glc
c2
Glu
c3
Gln
c4
Glyc
d1
His
d2
Ile
d3
Lac
d4
Leu
e1
Lys
e2
Met
e3
NH4
e4
Phe
f1
Pro
f2
Pyr
f3
Ser
f4
Thr
g1
Trp
g2
Tyr
g3
Val
Time (h)
0
100
200
0.5
1
1.5
experimental
train
experimental
test