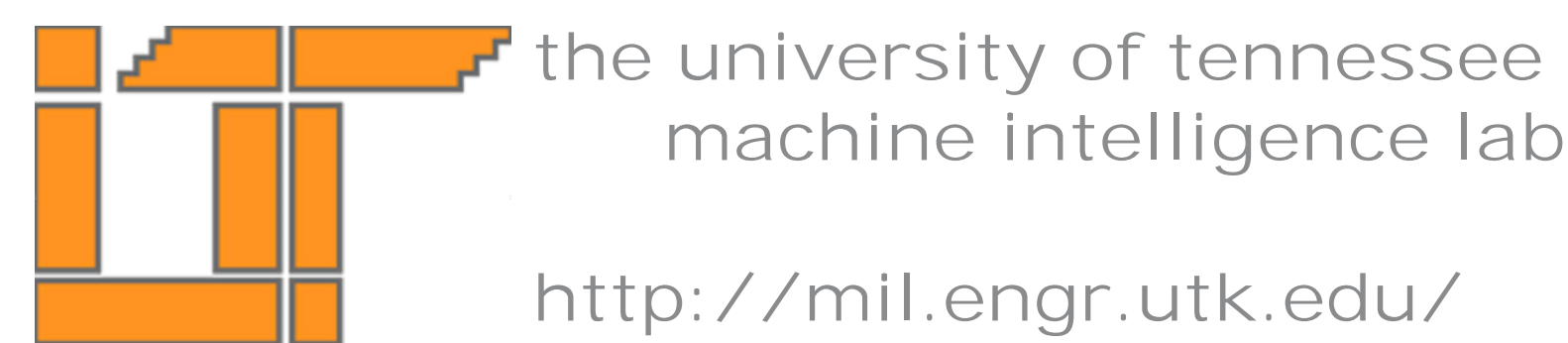


Functional analysis and prediction of tumor growth



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Abstract

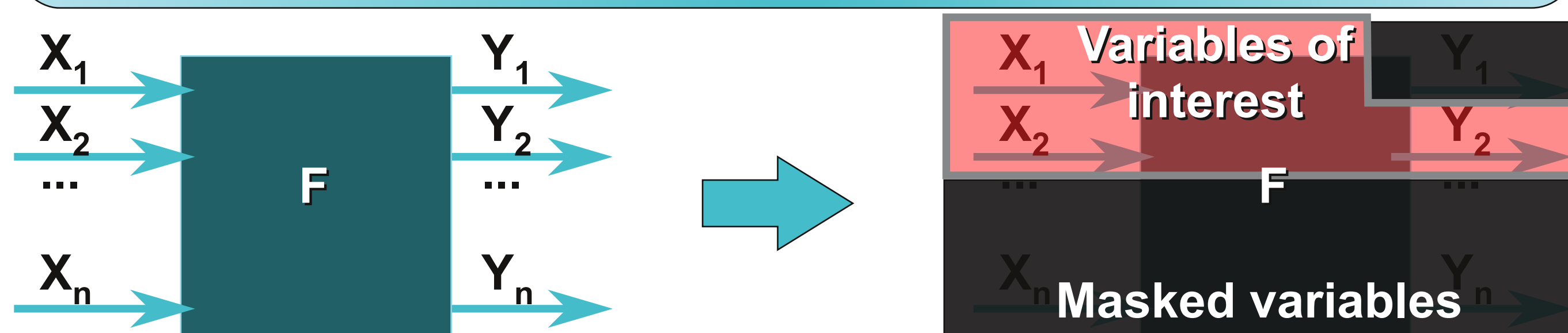
This work introduces a method for predicting tumor growth by:
 1) Identifying functional masks for the tumor with high predictive power
 2) Learning parameters that predict growth based on these masks

Given simulated tumor growth trajectories (presented as cancer cell counts for voxels within a 128x128 grid), we first examine a large number of trajectories in order to determine, for any given central voxel, which neighboring voxels have the highest predictive power in determining future states of the central voxel (we refer to these sets of predictive voxels as 'functional masks'). A novel functional analysis procedure is developed which uses an evolutionary algorithm combined with general systems theory principles in order to search for highly predictive functional masks. Probabilistic parameter estimation is then performed over the voxels in this functional mask in order to determine the probability distribution of the next state of the central voxel conditioned on the current and previous states of its neighbors. **Using this approach we are able to make accurate predictions of tumor growth using general methods that do not rely on biological or other domain-specific knowledge about the detailed mechanisms underlying the growth.**

	Simulation	Prediction
Time 10		
Time 50		
Time 80		

Actual and predicted tumor growth compared. Each prediction is calculated using the prior two time steps as input.

Functional Masks and System Theory



Functional masks represent hypothesis about input and output relationships among system variables of interest. The concept of a functional mask was introduced through Klir's system-theoretical work on the 'general systems problem solver' [3] and subsequent work in fuzzy inductive reasoning [2].

Functional Mask Search

The functional mask search was performed using an evolutionary algorithm to efficiently search the space of possible functional masks in order to find masks with high predictive power. The algorithm used is population-based incremental learning (PBIL) [1], which evolves a probability vector representing the probability with which each potential mask member is included in candidate masks.

The PBIL algorithm operates as follows:

- 1) Masks created by sampling from the probability vector
- 2) Each mask evaluated and given a fitness metric
- 3) The masks with the largest and smallest fitness values are used to adjust the vector to increase the probability of generating masks with large fitness values.
- 4) Repeat until a mask is found with 'good enough' fitness

We define the fitness of a mask in order to consider two things:

- (1) How accurately the predictions made by a mask are likely to be
- (2) How often a mask is likely to be able to make predictions

For (1), we calculate the proportion of the information entropy in the mask:

$$H_r(M) = 1 - \frac{H(M)}{H_{\max}} \quad H(M) = \sum_{vi} (p(I)H(I)) \quad H(I) = - \sum_{vn} (p(O_n|I) \log_2 p(O_n|I))$$

For (2), we calculate the 'observation ratio':

$$O_r(M) = \frac{5n_5 + 4n_4 + 3n_3 + 2n_2 + n_1}{5n_L} \quad \text{where } n_k \text{ is the number of observations occurring } k \text{ times and } n_{\text{leg}} \text{ is the total number of observations that could occur}$$

The total mask fitness is the product of these two measurements.

Growth Prediction

Once the best functional mask has been determined, we use a simulation trajectory to perform parameter estimation and calculate the next state probability distribution of a central voxel conditioned on the current state information of the voxels in the functional mask. In our experiments we separate the simulation trajectory's information into training and testing sets and use k-fold cross-validation to avoid bias caused by testing and training over the same data.

Experimental Results

The experiment performed analyzed 400 simulation trajectories of tumor growth for the functional analysis and then selected one for use in growth prediction. The cancer cell counts for each voxel were binned in one of 7 possible classes in order to handle the large input space.

For the functional analysis, a mask search was performed in order to select the best functional mask out of all voxels within a distance of 3 grid coordinates and 2 time steps in the past. The functional mask identified consisted of 5 voxels; 2 from the previous time step and 3 from two time steps in the past. The prediction task used frequency counts to estimate the probability of each possible class value for the next time step of a voxel based on the mask states.

Initial results are very promising:

- 98.3% accuracy over 1,300,000 predictions of next state
- 99.2% of predictions within one class of the correct class
- 95% accuracy when predicting two time steps in the future
- 96.3% of predictions within one class of the correct class

Figure above demonstrates prediction versus actual tumor growth.

Discussion and Future Directions

This represents the initial 'proof of concept' experimental results; the successful result indicates that the approach has some merit. The tumor growth model used was not the most complex model available; more research needs to be performed in order to explore analysis of more complex behavior and determine how much training data is needed to ensure accurate prediction.

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