

# Thesis Proposal

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## 1 Introduction

Resting-state functional MRI (rs-fMRI) is increasingly used for probing functional connectivity of the human brain. The spontaneous activity identified by rs-fMRI plays a key role in understanding the normal brain's functional organization. It also holds valuable diagnostic and prognostic information towards various neurological or psychiatric diseases including Alzheimer's disease, depression, schizophrenia, etc [1]. The blood oxygenation level-dependent (BOLD) signal of fMRI detects the locations of increased neuro activity by measuring the blood oxygen levels at consecutive time points. The higher the temporal correlation between two spatially distant regions, the more likely that there is a functional connection between those regions.

The analysis of rs-fMRI data is a challenging task, due to the scanner noise, physiological noise, head motion, and subject's random thoughts during data acquisition. Various techniques are proposed to address these issue. Among them, (1) spatial smoothing is used to increase the signal-to-noise ratio, and (2) group analysis is used to increase the statistical power by estimating an average functional network and to allow comparisons between groups. Both approaches have drawbacks that are to be elaborated in the next two paragraphs. In my work I address the issues concerning the above two aspects, with the focus on the latter.

In conventional functional connectivity studies, the spatial regularities of the connectivity are enforced by applying a smoothing filter as a preprocessing step. Depending on the noise level and the number of subjects in a group study, optimal kernel width of the filter may vary [2]. In current state-of-art processing pipeline, the kernel size is arbitrarily given a value ranging from 4mm to 10mm. This may introduce over-smoothing and pose difficulty in identifying connections between small regions, or introduce under-smoothing resulting in insufficient noise reduction. Moreover, the sub-optimal choice of the smoothing parameters can change the result drastically. There needs to be a statistical method that explicitly models the spatial smoothness of the connectivity patterns. The model should be data-driven in that the parameters are estimated from the fMRI images data under study.

In the group analysis, subjects may exhibit similar but not exactly same spontaneous BOLD fluctuation. Current group studies typically first identify each subject's connectivity sepa-

rately regardless of other subjects, and then estimate a *pooled* summary of the group connectivity map [3, 4], or estimate group map first and then back-reconstruct the subject network map [5]. Such approaches are sub-optimal, since estimation of one subject’s connectivity does not benefit from other subjects. From a Bayesian point of view, once the population distribution is known, it can help each subject’s estimation as a prior. Subjects network estimates also gives feedback on group estimation. We need a data-driven, unified probabilistic framework and put the connectivity variables of both group and subjects jointly into this model. Inference can be made from the posterior of the variables in both (subject and group) levels given the observed time series data.

Furthermore, the full Bayesian model provides us an opportunity to study the variability of the functional network by inference of the posterior. Besides the traditional variance and confidence interval analysis, the mode of spatial variability can be inferred from multivariate analysis. For the first time, to our best knowledge, it would be possible to visualize how functional homogeneous regions change along the principal direction of their posterior variability, and compare these change across subjects.

## 2 Thesis Statement

*A multilevel Markov Random Field model improves the reliability of the functional network estimation in rs-fMRI group study by taking into account context information as a prior. The data-driven Bayesian model can jointly estimate both population and subjects’ connectivity networks, as well as drawing inference on the uncertainty in the estimation, and on the variability across subjects.*

The phrase *Context* has two meanings: 1) The functional patterns of human brain is spatially coherent. Neighboring voxels have larger probability of being in the same functional network. 2) The network that a voxel belongs to in one subjects is dependant on the networks of the same voxels in other subjects. The patterns of functional networks from the rs-fMRI study are to some extent shared by multiple subjects, while the variability across subjects must be taken into account.

By *reliability* I mean the decrease in the variance of the functional networks that we estimate with different subsets of all subjects. The reliable estimates will be closer to the true network in simulation test, where we know the true answer.

## 3 Contributions

To test our statement, we propose the following contributions:

- **Full Pairwise Connectivity With Spatial Coherence.** I propose a method that

estimates pairwise functional connectivity in the whole brain of a single subject, without *a priori* knowledge of the seed region. The model needs to take into account the spatial context information, and learn the strength of the coherence from the data.

- **Identify Consistent, Spatially Coherent Multiple Functional Networks.** I propose a data-driven, generative model that can cluster the gray matter voxels of single subject’s brain into disjoint multiple functional networks, while respecting the spatial coherence of the voxels.
- **Hierarchical Model For Group Study.** I propose a hierarchical model that can estimate functional networks from a group of subjects. The model will estimate an overall group’s network map as well as individual subjects network maps at the same time. When Clustering the voxels into different networks, spatial neighbors both within and across subjects will be used in a prior of a Bayesian framework. The variability of each subject’s connectivity due to noise and artifact will be reduced to the extent that is to be determined automatically from the data.
- **Variability of Resting-State Functional Network.** Based on the hierarchical MRF model proposed above, I will draw inference on the variance and the confidence intervals of the functional network. I will test the variability of the network by using a subset of the data and perform bootstrap sampling. I also plan to explore and visualize the modes of spatial variability of the functional network patterns.

## 4 Literature Review

There are two fundamental principles in probing brain’s functional organization: *functional integration* and *functional specialization* [6]. Functional specialization means an anatomically segregated cortex region is specialized for some aspects of a mental process. A cortical infrastructure that support such process may involve many specialized areas. Functional integration says these areas do not exist in isolation, but are mediated by the information flows via the action potentials carried by axons, which are bundled into large fiber tracts.

fMRI is originally used for detect the neuro activity in experiments with task paradigm. It was found [7] that there are consistent patterns of activity even at subject’s resting state, when subjects do not receive any external stimulus during scan. In recent years the emphasis of neuroimaging is shifting from blobology (functional specialization/segregation) towards connectology (functional integration) [8], such spontaneous activity estimated from resting-state fMRI (rs-fMRI) have provide insight into the intrinsic architecture of the human brain.

The majority of functional neuroscience studies has a task or stimulus for the subject to conduct, and the resulting changes in neuro activity are measured. For data obtained in such experiments, the core methods such as Statistical Parametric Mapping (SPM) use general linear model [9] to test a null hypothesis, hence a hypothesis driven method. The effects of a stimulus signal is estimated as a multiple linear regression problem, with BOLD signal of stimulus as predictor variable, and BOLD signal of any brain voxel as response variables.

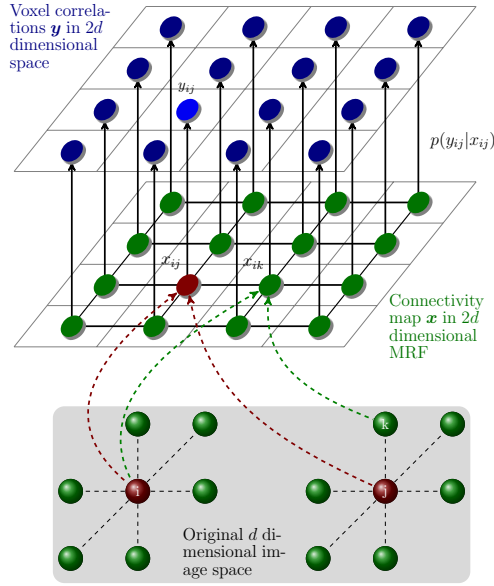


Figure 1: A MRF defined on high dimensional graph that model the pairwise connections of gray matter voxels. A node in the high dimension graph is defined as a pair of voxels in original image. an edge are added when any voxels in the two pair of voxels are spatially neighbors. This MRF is embedded into a generative model as a prior distribution, i.e. we suppose , a sample correlation is *generated* from the given random variable of connectivity or no connectivity. For inference of the connectivity given the observed sample correlation data, *Maximum a Posteriori* is used, together with the Gibbs Sampling and mean field theory approximation.

Activation or no activation is decided by the significance of the effects (i.e. regression coefficients) under the null hypothesis of no activation. This method is often regarded as mass univariate, in the sense that the effects of the stimulus on one voxel is independent on the effect of others, even they are spatially adjacent. In practice, a Gaussian filter is always applied for spatial smoothing in preprocessing step, and introduces dependence between spatially adjacent voxels' intensities (and also the effects of SPM).

In rs-fMRI study, the aim is to look for spontaneous neuro activity when there is no external input. Because of the lack of stimulus signal, the standard SPM method does not apply to the rs-fMRI data. New computational methods, sometimes called data-driven analysis, borrow technical concepts from many fields including machine learning and computer vision. These methods fall into a few categories [10] listed as below.

Seed-based methods look for the linear correlation between an *a priori* region-of-interest (ROI) and all other regions or voxels in the whole brain [11]. This approach is inherent simple, sensible, and easy to interpret. However, a *a priori* manual selection of ROI is required, and only one functional system can be detected at a time. In section 5.1 we propose a mixture model for connectivity analysis without the seed region as input [Liu10a]. This is to our knowledge the first work that can estimate all spatially coherent, pairwise connections in a single run.

Independent Component analysis (ICA) methods look for statistically independent components without the need of selecting ROI [12]. But users need to manually select meaningful component by visual inspection. Clustering-based methods partition the brain voxels into distinct regions (clusters), and voxels in same regions belong to same functional networks. If the goal is to discriminate the patients and healthy control groups, pattern classification method can also be used.

There are also graph theory based methods that treats each ROI (or voxel) as a node on the

graph, and the connectivity between them as edges, and a rich set of graph algorithms can be used to learn the graph structure (small-worldness, modularity, etc).

## 5 Methodology and Preliminary work

The main technical tool used in our series of work is the generative probabilistic model and Markov random field (MRF). To be specific, define a graph  $\mathcal{G} = (\mathcal{V}, \mathcal{E})$ , where  $\mathcal{V}$  is the set of nodes, with each node representing a single voxel in the image. An edge  $e = (s, r)$  is added to  $\mathcal{E}$  if the node  $s$  and  $r$  are spatial neighbors. The label of functional network that a voxel belongs to is defined by the random variable  $x_s \in \mathcal{L} = \{1, \dots, L\}$  that attached to each vertex  $s \in \mathcal{V}$ .

Two labels are correlated if they are spatially neighbor. The network label map  $x = (x_1, \dots, x_N)$  is a MRF because given the spatial neighbors of a voxel, its network label does not depend on the remaining voxels statistically. This local neighboring structure can be represented globally by a multivariate distribution

$$Prob(x) = \frac{1}{Z} \exp \left\{ -\beta \sum_{(s,r) \in \mathcal{E}} \delta(x_s, x_r) \right\}.$$

The function  $\delta(x_s, x_r)$  takes 1 when  $x_s = x_r$ , and takes 0 otherwise. By this definition, a label map with large regions of constant labels has higher probability. This will be used as a regularization prior in our Bayesian model. The applications of MRF in my work depends on the specific questions to answer. In [Liu10a], it is used as a prior distribution of a high dimensional MRF. In [Liu11a], it is used in a generative model for clustering. And in [Liu12a], the MRF is generalized to include both group labels and subject labels for solving a joint estimation problem.

### 5.1 Full Pairwise Connectivity With Spatial Coherence

Our first attempt [Liu10a] on detecting functional network aims to explicitly model the spatial smoothness of the network. In both task-based and resting-state fMRI the impact of imaging noise can be reduced by taking advantage of the spatial correlations between neighboring voxels in the image. A common approach used for instance in statistical parametric mapping (SPM)[9] is to apply a spatial Gaussian filter to smooth the signal prior to statistical analysis. However, this can lead to overly blurred results, where effects with small spatial extent can be lost and detected regions may extend beyond their actual boundaries. An alternative approach to spatial regularization that has been proposed for task activation paradigms is to use a Markov Random Field (MRF) prior [13, 14, 15, 16, 17], which models the conditional dependence of the signals in neighboring voxels.

We propose [Liu10a] to use MRF models in rs-fMRI to leverage spatial correlations in functional connectivity maps. Unlike previous MRF-based approaches, which use the neighbor-

hood structure defined by the original image voxel grid, the neighborhoods in functional connectivity must take into account the possible relationships between spatially distant voxels. Therefore, we define the neighborhood graph on the set of all voxel pairs. This results in a Markov structure on a grid with twice the dimensions of the original image data, i.e., the pairwise connectivities for three-dimensional images results in a six-dimensional MRF. The neighborhood structure is defined so that two voxels are more likely to be connected if they are connected to each other’s spatial neighbors. See figure 1 for an illustrative view.

We combine the Markov prior on functional connectivity maps with a likelihood model of the time series correlations in a posterior estimation problem. Furthermore, we model solve for the unknown parameters of the MRF and likelihood using an Expectation Maximization (EM) algorithm. In the estimation step the posterior random field is sampled using Gibbs Sampling and estimated using Mean Field theory.

Fig. 2 compares the real data results using no spatial regularization, Gaussian smoothing, and the proposed MRF model. Though the posterior connectivity of the MRF is computed between every pair of voxels within a slice, for visualization purposes, only the posterior of the connectivity between one voxel and the slice is shown. We chose to visualize the connectivity to a voxel in the posterior cingulate cortex (PCC) because this is known to be involved in the Default Mode Network [7], with connections to the medial prefrontal cortex (MPFC). The results show that Gaussian smoothing is able to remove noise, but is unable to find a clear connection between the PCC and the MPFC. Our proposed MRF model (rightmost plot) is able to remove spurious connections, and also clearly shows a connection to the MPFC.

It is noted that this approach does not need *a priori* knowledge of the ROI. Once the algorithm finishes, it outputs all the pairwise connectivity for all gray matter voxels. Putting this large connectivity matrix into a visualization tool, users can explore the functional networks with various seed regions and see the real-time results.

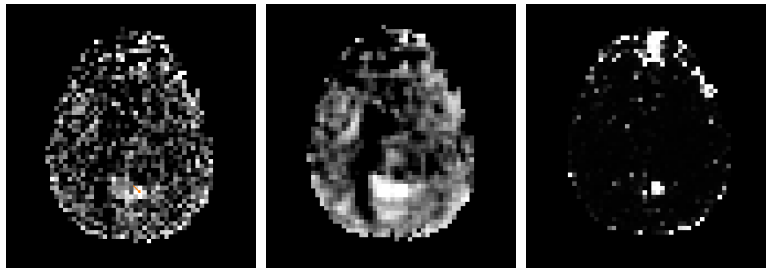


Figure 2: Correlation map and Posterior Connectivity map between seed voxel and slice containing the seed. From left to right: the correlation map computed from data without spatial smoothing; correlation map of data after smoothing; Posterior probability computed from MRF.

## 5.2 Identify Consistent, Spatially Coherent Multiple Functional Networks

The above method in section 5.1 is able to detect functional networks such as default mode network, there are two issues that have to be addressed. 1) With one seed region at a time, only one functional system can be shown. The functional architecture would be better understood if multiple systems are shown together in the same image. 2) The computation cost is huge, mostly due to the high dimensional graph and the optimization problem. This is partly mitigated by a GPU implementation in current single subject analysis, but would be difficult for generalizing to group study.

One possible solution is to employ clustering techniques to automatically partition the brain into functional networks. In such methods, a similarity metric is defined first, e.g., correlation [18] or frequency coherence [19], and then a clustering method such as  $k$ -means or spectral clustering is used to group voxels with similar time series. A drawback of these approaches is that they disregard the spatial position of voxels, and thus ignore the fact that functional networks are organized into sets of spatially coherent regions.

We introduce a new data-driven method [Liu11a] to partition the brain into spatial coherent, non-overlapping networks of functionally-related regions from rs-fMRI. The proposed algorithm does not require specification of a seed, and there is no ad hoc thresholding or parameter selection. We make a natural assumption that functionally homogeneous regions should be spatially coherent. Our method incorporates spatial information through a Markov random field (MRF) prior on voxel labels, which models the tendency of spatially-nearby voxels to be within the same functional network.

We notice the mean intensity and the variance (both over all the time points) of the time course at each voxel is not an indicator whether they belong to same functional network, so each time series is first normalized to zero mean and unit norm, which results in data lying on a high-dimensional unit sphere. We then model the normalized time-series data as a mixture of von Mises-Fisher (vMF) distributions [20]. Each component of the mixture model corresponds to the distribution of time series from one functional network.

Solving for the parameters in this combinatorial model is intractable, and we therefore use a stochastic method called Monte Carlo Expectation Maximization (MCEM), which approximates the expectation step using Monte Carlo integration. The stochastic property of MCEM makes it possible to explore a large solution space, and it performs better than a standard mode approximation method using iterated conditional modes (ICM).

The proposed method is related to previous approaches using MRFs to model spatial relationships in fMRI data. Descombes et al. [14] use a spatio-temporal MRF to analyze task-activation fMRI data. Our previous methods [Liu10a] use an MRF model of rs-fMRI to estimate pairwise voxel connections. However, neither of these approaches tackle the problem of clustering resting-state fMRI into functional networks.

The linear correlation between two time series in original image space is equivalent to the inner product of two points on the sphere. MRF is again used as a spatial smoothness prior



on the hidden network labels. We estimate the network labels by maximizing its posterior probability in a EM framework, such that voxels with same estimated labels have larger inner product, which amounts to have larger correlation in original space and belong to same functional network. The introduction of MRF again poses the difficulty of computing the expectation directly, We use Monte-Carlo Sampling to approximate the expectation value in EM. By this method [Liu11a] we are able to detect most significant brain networks like motor, visual, motion, salience and executive control, and default mode network with precision and consistency competitive to standard ICA method, as can be found in figure 3.

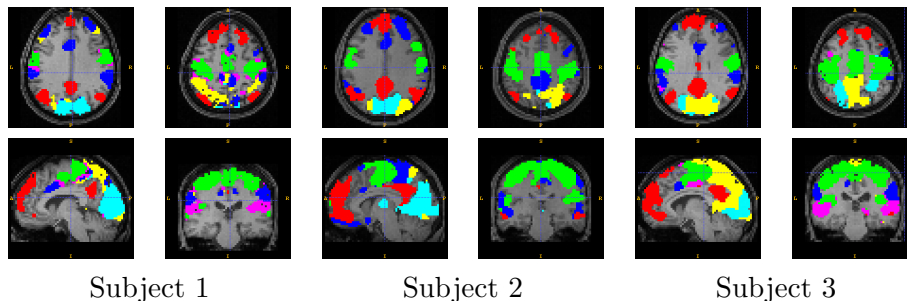


Figure 3: Functional networks detected by the proposed method for 3 subjects overlaid on their T1 images. The clusters are the visual (cyan), motor (green), executive control (blue), salience (magenta), dorsal attention (yellow), and default mode (red) networks.

### 5.3 Current Work: Hierarchical Model For Group Study

The availability of large rs-fMRI databases opens the door for systematic group studies of functional connectivity. It is a natural assumption that a group of subjects must share similar patterns of functional connectivity, while keeping individual subject’s variability. Such variability may come from subject random thoughts, despite that they are instructed not to think anything specifically. While the inherently high level of noise in fMRI makes functional network estimation difficult at the individual level, combining many subjects’ data together and jointly estimating the common functional networks is more robust. However, this approach does not produce estimates of individual functional connectivity. Such individual estimates are an important step in understanding functional networks not just on average, but also how these networks vary across individuals.

The method we propose in above section [Liu11a] works specifically on single subject analysis, and my next aim is to build a model that estimate functional networks among a group of subjects. Most current studies estimate the networks in a sequential approach, i.e., they identify each individual subject’s network independently to other subjects, and then estimate the group network from the subjects networks. This one-way flow of information prevents one subject’s network estimation benefiting from other subjects.

Group ICA [12] is a generalization of ICA to multiple subjects, in which all subjects are assumed to share a common spatial component map but have distinct time courses. The



time courses from all subjects are concatenated temporally, followed by a single ICA. Although the subject component maps are obtained by a back-reconstruction procedure, there is no explicit statistical modeling of the variability between the group and subject component maps. Ng et. al [21] use group replicator dynamics (RD) to detect subject’s sparse component maps, with group information integrated into each subject’s RD process. In clustering-based methods, the subjects clusterings are usually averaged to obtain a group affinity matrix and are followed by a second level clustering on the group similarity matrix [22, 3]. Because the group level clustering is conducted after subject level clustering, the clustering of one subject is unaware of the information from other subjects, as well as the group clustering.

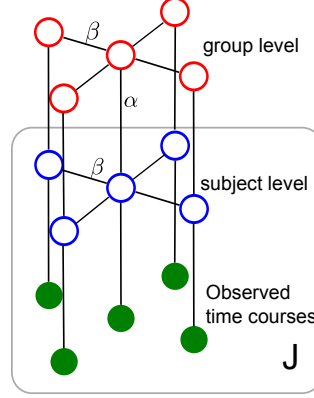


Figure 4: Left: Hierarchical MRF depicted by undirected graph. The  $J$  subjects are compactly represented by a box with label  $J$ .  $\alpha$  and  $\beta$  are parameters that represent the strength of the statistical dependencies between the nodes.

We propose a Bayesian hierarchical model [Liu12a] to identify the functional networks from rs-fMRI that includes both subject and population levels. We assume a group network label map that acts as a prior to the label maps for all subjects in the population. This Bayesian perspective provides a natural regularization of the estimation problem of a single subject using information from the entire population. The variability between the subjects and group are taken into account through the conditional distributions between group and subjects. The within-subject spatial coherence is again modeled by a MRF. The group and all subjects network map are connected into a larger graph, with edges between corresponding voxels between group and subjects, and between adjacent voxels within single subjects. See figure 4 for the model illustration.

The concept of this hierarchical model is similar to the multi-level modeling of linear regression. Estimation of the functional network on single subject corresponds to no pooling since it fits a model for each subject separately. A sequential approach of estimating group network after subjects networks is like complete pooling, since it ignores the group information when estimating subjects network. And our hierarchical MRF model corresponds to the partial pooling, i.e., the multi-level model where a tradeoff defined by a pooling factor, or a shrinkage factor. Compared to the *pooled* averaging method, our hierarchical model respects the individual variability, hence also better estimates the group’s functional network.

Both the group clustering and subject clusterings are estimated simultaneously with a Monte Carlo Expectation Maximization (MCEM) algorithm. The model is data-driven in that all parameters, regularized by two given hyper-parameters, are estimated from the data, and the only parameter that must be specified is the number of networks.

Ours is the first hierarchical MRF applied to fMRI for modeling both group and individual networks. The model of Ng et al. [23] combines all subjects into a single MRF and bypasses the need for one-to-one voxel correspondence across subjects, but the edges are added directly between subjects without a group layer. In our model, a group layer network map is explicitly defined, and the consistency between subjects is encoded through adding edges between group and subjects labels. Our method differs from other clustering methods [22, 3] in that their methods identify the subject’s functional network patterns independently, without any knowledge of other subjects or group population. Instead, our method estimates both levels of network patterns simultaneously. The proposed approach can be seen as a counterpart on the clustering branch of the multi-subject dictionary learning algorithm [24], which also has a hierarchical model and a spatially smoothed sparsity prior on the group component map.

## 5.4 Variability of Resting-State Functional Network

The hierarchical MRF model decreases the scanner noise, physiological noise and other artifacts, but does not spoil the true signal. The variability of the functional connectivity due to individual subject’s spontaneous thoughts is believed to be part of the true signal that we want to keep and explore. Given the Bayesian model we proposed in section 5.3, a multivariate posterior distribution of the connectivity variables is available as a summary of our current state of knowledge (arising from both the observed data and the MRF prior opinions). A standard point estimate would just report a single value (mean, mode or median) for each variable. However, when the sample size is small, and number of variables is large (which is the case in fMRI study), it is inappropriate to summarize inference by one value, especially when the summary is used for clinical decision. We need to measure the uncertainty and variability of the estimates. Uncertainty means the variance of the connectivity variables inferred from the posterior density. Variability means the change of the spatial patterns because of single variable’s uncertainty and the difference across subjects.

Because the lack of analytic solution of posterior distribution, obtaining the uncertainty of single variable is not straightforward. However, by using the Markov Chain Monte-Carlo tool we developed in previous work, we are able to draw samples of the connectivity variables from the posterior, and estimate the variance from the samples.

Given the uncertainty on the voxel level, the more interesting question is the variability on the network level. Here I want to find the most dominant pattern of change of a functional network over subjects, as well as over the uncertainty of single voxels. For example, does the PCC’s size and shape change over all subjects mainly happen along the dorsal-ventral direction, or the anterior-posterior direction? We can see the functional network patterns as objects with certain shape and size. The change of the shape or size can be represented by the multivariate analysis method such as Principal Component Analysis.

## 6 Timeline

Based on the my current work and the contributions that I will work on, I give the schedule for the remaining time of the thesis work:

- **Fall 2012:** Network variability analysis.
- **Spring 2013:** Submit a journal paper on the hierarchical model in section 5.3. Continue on variability analysis.
- **Summer 2013:** Dissertation writing and Ph.D thesis defense.

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## List of Publications

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